comments to section 106.3(s) that the term "responsible party" be used to designate the primary manufacturer and be incorporated into the regulations wherever appropriate. Thus, throughout subpart 106.97, dealing with assurances for quality factors, the term "or responsible party" should be inserted after each reference to the manufacturer's responsibility to provide such assurances.

Whenever the language "When fed as the sole source of nutrition" is used, it should be followed by "or as otherwise represented," in order to allow for formulas represented for use only with older infants.

The IFC also suggests adding to the Agency's description of adequate growth the important qualification that "expected" be interpreted in the context of the population for whom the formula is intended. The expectation that infant formulas "shall be capable of supporting normal physical growth of infants" will vary dependent upon the population. Some targeted populations have medical conditions whose "normal physical growth" would be "expected" to be different from that of infants without a medical condition, in the same way as a premature population cannot be compared to a full-term population. Although many of these formulas can be covered within the special infant formula requirements, it would be best if the broader goal were stated in a way that will be suitable for all situations – e.g., "expected physical growth."

It would not be possible to achieve a reasonable scientific consensus on what additional functions might constitute "healthy growth" as it is related to nutrition. And, while a manufacturer may choose to assess functions beyond anthropometric growth (especially if promotional claims are to be made regarding the use of the new formula), there are no generally accepted and validated methods for assessing "healthy" growth beyond the anthropometric measures. Many of the tests that might be used were originally designed to detect individuals with clinically impaired functions; not to distinguish or attribute significance to the small differences between individuals or groups, which may be seen in clinical studies of generally healthy populations.

The AAP consultation did describe means and possible indications for testing certain key nutrients, which may be affected by changes in ingredient form or processing. The Agency specifically requested comments on the feasibility of certain of the AAP's suggestions, and our detailed comments are provided at the close of our discussion of this subpart. Suffice it to say, here, that while we agree with the Agency as to the importance of assessing substantive changes in the manufacturing process on nutrient bioavailability, a broader definition of growth does not achieve this objective. And, while the future introduction of novel ingredients in infant formula (such as components of human milk not presently in infant formulas) may present new challenges to the regulatory process, introducing ambiguity and subjectivity into these regulations is not an appropriate means of responding to this challenge. Any safety concern with regard to a new ingredient is better handled under the regulatory rubrics specifically designed for ingredient evaluation.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(i) The manufacturer shall:<br><br>106.97(a)(1)(i)(A) Conduct a clinical study that is no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study. | Delete.<br><br>Delete. |

IFC Redlined Version

~~106.97(a)(1)(i) The manufacturer shall:~~

~~106.97(a)(1)(i)(A) Conduct a clinical study that is no less than 4 months in duration, enrolling infants no more than 1 month old at time of entry into the study.~~

IFC Comment

Regarding IFC's recommended deletion of these proposed regulations, see General Comments on Assessment of Normal Growth. IFC offers comments on all the following proposed regulations falling under section 106.97(a)(1) with the caveat that clinical growth studies should be conducted for the purpose of demonstrating bioavailability only when they are the most appropriate, and any specifics as to the nature and scope of such a study should be incorporated into agency Guidance rather than a regulation.

See the IFC General Comment regarding Definition of Manufacturer. As discussed in the previous comment, the term "or responsible party" should be added after each reference to the manufacturer's responsibility to provide assurances of quality factors.

In the Agency's April 2003 announcement of the reopening of the comment period, FDA specifically requested comment on proposed section 106.97(a)(1)(i)(A), to address the FAC recommendation that infants be enrolled by 14 days of age. The SCF Committee proposed in 1993 that the nutritional adequacy of all products should be demonstrated by a longitudinal study on weight and height development over at least 3 months, involving at least 20 babies born at full term and aged less than one month at the beginning of the study. This study should include, if necessary, data on plasma levels of albumin and short half-life proteins, and on the plasma amino acid profile. Consequently, the selection of 16 weeks or 3 months, or 4 months as originally proposed by FDA are proposed on the basis of convenience and current well-baby visit schedules, not on the basis of scientific assessments of sensitivity, validity or the relationship of growth over this period to health. Growth studies are usually conducted from approximately 14 days after birth, which coincides with routine pediatric visits until the infant is approximately 112 days of age or about 4 months of age (i.e., study duration of 98 days). Days of age versus weeks or months of age are used to simplify the calculation of study visits.

IFC believes that the design of the study should address the specific objectives of the study. If nutritional adequacy of a formula to be fed during the first year of life is to be assessed, as measured by weight gain, (per 1988 CON/AAP guidelines) then the study should be initiated within the first month of life. However, if the formula is for a different age range, then the design of the study should reflect this difference. For routine growth studies,

infants would ideally be enrolled by approximately 14 days of age and study measurements (growth) measured at approximately 14, 28, 56, 84 and 112 days of age. However, we are aware of no biological reason why any enrollment age short of one month should be considered to disqualify an infant from such a study. The primary outcome is growth, expressed as weight gain in g/day (14-112 days). Secondary outcomes are body weight expressed as attained weight (interval gains) and attained body length. There is a rationale for inclusion of infants at not later than 14 days of age, because this early time is the time of greatest nutrient requirement and greatest sensitivity to nutrient adequacy. It may be preferable to study growth velocity (g/kg/d), which is yet more sensitive than absolute g/d, thus requiring fewer infants to achieve the same sensitivity (Butte et al.).

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(i)(B) Collect and maintain data in the study on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and average daily weight increment, and plot the data on National Center for Health Statistics (NCHS) reference percentile body weight and body length curves. The NCHS growth charts are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Constituent Operations (HFS-565), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, may be examined at the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or the Office of the Federal Register, 800 North Capitol St. NW, Suite 700, Washington, DC. | Delete. |

IFC Redlined Version

~~106.97(a)(1)(i)(B) Collect and maintain data in the study on anthropometric measures of physical growth, including body weight, recumbent length, head circumference, and average daily weight increment, and plot the data on National Center for Health Statistics (NCHS) reference percentile body weight and body length curves. The NCHS growth charts are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Constituent Operations (HFS-565), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, may be examined at the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or the Office of the Federal Register, 800 North Capitol St. NW, Suite 700, Washington, DC.~~

IFC Comment

When AAP-CON provided its 1988 consultation, it recommended rate of weight gain as the anthropometric parameter for assessing physical growth because it was felt to be most

sensitive and, therefore, more appropriate. (Indeed, the AAP Handbook on Nutrition maintains that "average daily weight increment" alone provides a sufficient anthropometric measure of growth.) While collection of data on recumbent length and head circumference are often obtained simultaneously, their interpretation is generally secondary as recumbent length measurements at this age are associated with considerable error and head circumference is rather resistant to small differences in nutritional status. This science has not changed since the 1988 AAP-CON consultation. Thus, the IFC believes that it would be advisable to simplify both the collection of this data by manufacturers, and its review by the Agency, by requiring only those data considered to be the most sensitive, reliable and appropriate for measuring growth. We recommend that recumbent length continue to be measured as part of the standard growth protocol, allowing for calculation of BMI and some body composition measures as needed, but that these data need not be routinely reported to the Agency.

A randomized clinical study, with or without reference to an outside standard (e.g., Iowa reference data or CDC/NCHS reference standard), is the best method to assess whether infants receiving different feeding regimens differ in terms of a primary outcome parameter. A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human subjects (Fundamentals of Clinical Trials, 1985, Friedman LM, Furberg CD, DeMets DL). This research methodology is recognized as the most definitive method of determining whether and intervention has the postulated effect. The universally agreed reference population that defines healthy growth, infants breast fed by well-nourished mothers, cannot be included in a randomized trial.

Since the CDC/NCHS reference standards were recently revised, and since new science is constantly accumulating which may impact our changing understanding of what constitutes expected physical growth, it would be shortsighted to tie the assessment *only* to the currently existing reference standards. In the Agency's April 2003 announcement of the reopening of the comment period, it requested comments on whether manufacturers should still compare their clinical study growth data with the National Center for Health Statistics (NCHS) growth charts. The FAC considered other sources of reference data in addition to the NCHS. FDA states that the FAC "recommended the Iowa reference data as the most appropriate reference data for comparison because they are longitudinal, collected over the time period of interest for clinical studies of infant growth, and collected in a research setting." Our own recollection of the discussion was not so definitive. Several potential comparison references were discussed, and while all shed some light on what constituted expected physical growth, none was found to be dispositive.

The Iowa reference data, while excellent, may be less accessible than the CDC/NCHS growth charts, and the growth charts do incorporate some mechanism for quantitative assessment of growth patterns. However, the use of individual growth charts is not appropriate to establish whether one group of infants differs from another group of infants in terms of growth rates (as described by the 1988 CON/AAP guidelines). In general, the use of growth curves and historical databases are considered references, not standards. Furthermore, the use of curves to evaluate growth of infants could lead to inappropriate conclusions concerning normal growth. (The Use of NCHS and CDC Growth Charts in Nutritional Assessment of Young Infants, 2002, Grummer-Strawn LM on behalf of the CDC Growth Chart Working Group.)

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(i)(C) Collect anthropometric measurements at the beginning of the clinical study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the conclusion of the study. | Delete. |

IFC Redlined Version

~~106.97(a)(1)(i)(C) Collect anthropometric measurements at the beginning of the clinical study, at 2 weeks, at 4 weeks, at least monthly thereafter, and at the conclusion of the study.~~

IFC Comment

The frequency of body weight measurements is a protocol detail that should be provided in clinical study Guidelines, not regulations. Further, the proposed frequency of measurement is unnecessarily burdensome to parents facilitating their infants' participation in growth studies, since several of these times do not coincide with a regularly scheduled well-baby visit. Clinical trials for new formulas are often delayed because of the difficulty of recruiting sufficient numbers of participants.

In 2002, representatives of the infant formula industry prepared a sample clinical growth study protocol (Attachment M). The days of age represented above were selected as reasonable time intervals to assess growth and to coincide with routine pediatric visits. Thus, the changes indicated above should provide ample data to demonstrate expected physical growth without introducing added difficulties for the participants.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(ii) The clinical study protocol should: | Delete. |
| 106.97(a)(1)(ii)(A) Describe the scientific basis and objectives of the study, the planned control and treatment feeding regimens, the entrance criteria used to enroll infants in the study, the method of randomization used for the assignment of infants to feeding groups, the collection of specific measurements and other data, the methods used to limit sources of bias, and the planned methods of statistical analysis; | Delete. |

IFC Redlined Version

~~106.97(a)(1)(ii) The clinical study protocol should:~~

~~106.97(a)(1)(ii)(A) Describe the scientific basis and objectives of the study, the planned control and treatment feeding regimens, the entrance criteria used to enroll infants in the study, the method of randomization used for the assignment of infants to feeding groups, the collection of specific measurements and other data, the methods used to limit sources of bias, and the planned methods of statistical analysis;~~

IFC Comment

IFC understands from the April 2003 announcement of the reopening of the comment period that the Agency intends to remove references to clinical protocols from the proposed rule and to develop a guidance document instead on what it recommends be included in a clinical study protocol for infant formula that is submitted as part of an infant formula notification under section 412(c) of the act. We support the Agency's position that it is more appropriate to include information about clinical study design protocols in a guidance document rather than a regulation. By codifying it in a regulation, it will be much more difficult for modifications to be made that are reflective of the current scientific practices for conducting clinical studies.

We have attached the representative protocol that we developed for submission to the FAC as an example of what industry recommends be included in a clinical study protocol for infant formula that is submitted as part of an infant formula notification under section 412(c) of the act, in hope it will be considered in the development of that guidance document (Attachment M).

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(ii)(B) Describe the necessary qualifications and experience of investigators; | Delete. |
| 106.97(a)(1)(ii)(C) Be reviewed and approved by an Institutional Review Board (IRB) in accordance with part 56 of this chapter. The manufacturer shall establish procedures to obtain written informed consent from parents or legal representatives of the infants enrolled in the study in accordance with part 50 of this chapter; | Delete. |

IFC Redlined Version

~~106.97(a)(1)(ii)(B) Describe the necessary qualifications and experience of investigators;~~

~~106.97(a)(1)(ii)(C) Be reviewed and approved by an Institutional Review Board (IRB) in accordance with part 56 of this chapter. The manufacturer shall establish procedures to obtain written informed consent from parents or legal representatives of the infants enrolled in the study in accordance with part 50 of this chapter;~~

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. As discussed in previous comments, the term "or responsible party" should be added after each reference to the manufacturer's responsibility to provide assurances of quality factors.

The IFC's suggested substitution of the term "documented" for "written" to describe informed consent requirements is intended to accommodate instances involving illiterate parents who receive informed consent orally and acknowledge their desire for their child to

participate. While this practice may be interpreted as being in compliance with the requirement for "written informed consent," the IFC feels that a simple word change would clarify the acceptance of such situations.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(ii)(D) Explain how the study population represents the population for which the new infant formula is intended and how the study addresses the intended conditions of use of the formula. | Delete. |

IFC Redlined Version

~~106.97(a)(1)(ii)(D) Explain how the study population represents the population for which the new infant formula is intended and how the study addresses the intended conditions of use of the formula.~~

IFC Comment

IFC concurs with FDA that this belongs in the Guidance.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(ii)(E) Describe the sample size calculations and the power calculations and the basis for selecting the sample size and study design; | Delete. |
| 106.97(a)(1)(ii)(F) Describe the plan to identify and evaluate any adverse effects; | Delete. |
| 106.97(a)(1)(ii)(G) Describe the quality control procedures used to ensure the validity and reliability of the measurements collected. | Delete. |

IFC Redlined Version

~~106.97(a)(1)(ii)(E) Describe the sample size calculations and the power calculations and the basis for selecting the sample size and study design;~~

~~106.97(a)(1)(ii)(F) Describe the plan to identify and evaluate any adverse effects;~~

~~106.97(a)(1)(ii)(G) Describe the quality control procedures used to ensure the validity and reliability of the measurements collected.~~

IFC Comment

The language of these proposed regulations is acceptable as proposed for incorporation into agency Guidance, in that it describes appropriate quality control measures for discussion in any growth study protocol. The statements in the preamble, however, seem not to be related to the purposes of clinical study quality control as the IFC understands them. Quality control relates to the procedures used to assure that the data are accurate and appropriately obtained, while the statements in the preamble appear to speak to the choice of

appropriate endpoints in a clinical study. The two should not be confused, and the preamble to the final rule should clarify this. Serious adverse events are better defined and more important than capturing all adverse effects that may occur in the course of a study as most are not product related. In addition, many manufacturers will be driven to assess measures of infant formula 'tolerance' as a study outcome rather than adverse effects.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(ii)(H) Describe and compare the composition of the test and control formulas. | Delete. |

IFC Redlined Version

~~106.97(a)(1)(ii)(H) Describe and compare the composition of the test and control formulas.~~

IFC Comment

As discussed with respect to 106.97(a)(1)(ii)(A), there may be situations in which a reference appropriate to establishing that an infant formula supports acceptable growth can also function as a non-concurrent control in the study itself. In such a case, there would be no "control formula" to describe.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(1)(ii)(I) Describe the basis upon which the test formula is appropriate for use in evaluating the formula that the manufacturer intends to market, if the test formula used in a study is not identical to the formula that is intended to be marketed in the United States. | Delete. |

IFC Redlined Version

~~106.97(a)(1)(ii)(I) Describe the basis upon which the test formula is appropriate for use in evaluating the formula that the manufacturer intends to market, if the test formula used in a study is not identical to the formula that is intended to be marketed in the United States.~~

IFC Comment

IFC concurs with FDA that this belongs in the Guidance.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(a)(2) The manufacturer may request an exemption from the requirements of paragraph (a)(1) of this section if: | Delete. |
| 106.97(a)(2)(i) The manufacturer has similar experience using an ingredient, an ingredient mixture, or a processing method in the production of an infant formula marketed in the United States and can demonstrate that infant formula made with that ingredient, ingredient mixture, or processing method meets the quality factor requirements in Sec. 106.96; | Delete. |
| 106.97(a)(2)(ii) The manufacturer markets a formulation in more than one form (e.g., liquid and powdered forms) and can demonstrate that the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting nutrient content and bioavailability; | Delete. |
| 106.97(a)(2)(iii) The manufacturer can demonstrate that the requirements of paragraph (a)(1) of this section are not appropriate for evaluation of a specific infant formula, and that an alternative method or study design for showing that the formula supports healthy growth in infants fed it as their sole source of nutrition is available. | Delete. |

IFC Redlined Version

~~106.97(a)(2) The manufacturer may request an exemption from the requirements of paragraph (a)(1) of this section if:~~

~~106.97(a)(2)(i) The manufacturer has similar experience using an ingredient, an ingredient mixture, or a processing method in the production of an infant formula marketed in the United States and can demonstrate that infant formula made with that ingredient, ingredient mixture, or processing method meets the quality factor requirements in Sec. 106.96;~~

~~106.97(a)(2)(ii) The manufacturer markets a formulation in more than one form (e.g., liquid and powdered forms) and can demonstrate that the quality factor requirements are met by the form of the formula that is processed using the method that has the greatest potential for adversely affecting nutrient content and bioavailability;~~

~~106.97(a)(2)(iii) The manufacturer can demonstrate that the requirements of paragraph (a)(1) of this section are not appropriate for evaluation of a specific infant formula, and that an alternative method or study design for showing that the formula supports healthy growth in infants fed it as their sole source of nutrition is available.~~

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer and Premarket Notification. The provision that an exemption "may be available" based on a requirement to

"demonstrate" that a manufacturer or responsible party has experience with an ingredient, an ingredient mixture, or a processing method constitutes premarket approval, not notification. Since 1986, FDA has permitted manufacturers to make the determination contemplated by this section, and the IFC is not aware of any problems that have been created.

The Agency's April 2003 announcement of the reopening of the comment period asked for comments regarding what requirements the Agency should establish to determine when manufacturers must conduct clinical growth studies for a new or reformulated infant formula. IFC believes that there are instances when clinical studies may be necessary as proposed by IFC in section 106.120(b)(6). Thus, the "exemptions" provided in this proposed rule – as amended by our suggested changes – better describe those situations that would not trigger the need for a clinical growth study. In 2002, U.S. Infant Formula Manufacturers developed the "Decision Tree for Documentation of Nutritional Adequacy of a New or Change Infant Formula" (Attachment K) and "Decision Tree Chart for Documentation of Nutritional Adequacy of a New or Changed Infant Formula," (Attachment L) for consideration by the FAC, to which the Agency refers in its April announcement. These documents discuss, in greater detail, various changes to infant formula and the documentation required for such changes to support nutritional adequacy. These documents are appended here, as well, for agency consideration.

The IFC also believes that "similar experience" should be relevant, regardless of whether it occurred in the United States or elsewhere.

IFC believes that the choice of the representative formula should not be based solely on greatest adverse nutrient effect. For example, if a product has two forms, one a liquid, ready-to-feed formula for hospital use only, and the other a powder formula for retail use, it may be more appropriate to study the form that is intended for long term use (i.e., the powder) as opposed to the very short term formula (i.e., the liquid), which actually may have the greatest nutrient effect. The IFC believes that the manufacturer must be given responsibility for determining the most representative form to test.

On those occasions when studies have already been carried out on a form of the product, which meets neither of the above criteria, but cannot reasonably be expected to differ significantly from the form in question (in terms of nutrient levels or availability), those studies should also be able to provide the basis for exemption from additional studies. To require duplicative studies on forms of a product which do not differ significantly would be difficult to justify on an ethical basis.

The IFC appreciates FDA's recognition of the flexibility necessary to accommodate different products as well as evolution in clinical study design. Also, it should be noted that a formula may not necessarily be intended as a "sole source of nutrition" and consideration should be given to those situations in this paragraph.

"Healthy growth" should be changed to the alternative term, "expected physical growth," since the latter is the more meaningful term and the more objectively measurable criterion.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(b) Specific quality factor for protein quality of infant formula.<br><br>106.97(b)(1) The manufacturer shall collect and maintain data that establish that the biological quality of protein in an infant formula is sufficient to meet the protein requirements of infants. The manufacturer shall establish the biological quality of the protein in its infant formula by demonstrating that the protein source supports adequate growth using the Protein Efficiency Ratio (PER) rat bioassay described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," 16th ed., sections 43.3.04 and 43.3.05, "AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay" which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., Suite 500, Gaithersburg, MD 20857, or the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW, Washington, DC. If the manufacturer is unable to conduct a PER rat bioassay because of the composition of the protein in the formula, then it shall demonstrate that the amino acid composition of the protein meets the known amino acid requirements of infants for whom the formula is intended. | Acceptable; Renumbered 106.97(a).<br><br>106.97(a)(1) The manufacturer or responsible party shall collect and maintain data that establish that the biological quality of protein in an infant formula is sufficient to meet the protein requirements of infants. The manufacturer or responsible party shall establish the biological quality of the protein in its infant formula with any AOAC approved method, including the Protein Efficiency Ratio (PER) rat bioassay described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," 16th ed., sections 43.3.04 and 43.3.05, "AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay" which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., Suite 500, Gaithersburg, MD 20857, or the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW, Washington, DC. If the manufacturer is unable to conduct a PER rat bioassay because of the composition of the protein in the formula, then it shall demonstrate that the amino acid composition of the protein meets the known amino acid requirements of infants for whom the formula is intended. |

IFC Redlined Version

106.97(~~b~~a) Specific quality factor for protein quality of infant formula.

106.97(~~b~~a)(1) The manufacturer or responsible party shall collect and maintain data that establish that the biological quality of protein in an infant formula is sufficient to meet the protein requirements of infants. The manufacturer or responsible party shall establish the biological quality of the protein in its infant formula with any AOAC approved method, including ~~by demonstrating that the protein source supports adequate growth using~~ the Protein Efficiency Ratio (PER) rat bioassay described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," 16th ed., sections 43.3.04 and 43.3.05, "AOAC Official Method 960.48 Protein Efficiency Ratio Rat Bioassay" which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., Suite 500, Gaithersburg, MD 20857, or the Office of Special Nutritionals (HFS-456), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW, Washington, DC 20204, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW, Washington, DC. If the manufacturer is unable to conduct a PER rat bioassay because of the composition of the protein in the formula, then it shall demonstrate that the amino acid composition of the protein meets the known amino acid requirements of

infants for whom the formula is intended.

IFC Comment

IFC believes that the regulations should recognize other AOAC methods as they become available.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.97(b)(2) The manufacturer may request an exemption from the requirements of paragraph (b)(1) of this section if: | Acceptable; Renumbered as 106.97(a)(2). |
| 106.97(b)(2)(i) The protein source, including any processing method used to produce the protein source, is already used in another infant formula marketed in the United States, manufactured by the same manufacturer, and the manufacturer can demonstrate that such infant formula meets the quality factor requirements prescribed in Sec. 106.96; | Acceptable; Renumbered as 106.97(a)(2)(i). |
| 106.97(b)(2)(ii) The protein source, including any processing methods used to produce the protein source, is not a major change from the infant formula it replaces, and the manufacturer can demonstrate that the infant formula it replaces meets the quality factor requirements prescribed in Sec. 106.96. | Acceptable; Renumbered as 106.97(a)(2)(ii). |

IFC Redlined Version

106.97(~~b~~a)(2) The manufacturer may request an exemption from the requirements of paragraph (b)(1) of this section if:

106.97(~~b~~a)(2)(i) The protein source, including any processing method used to produce the protein source, is already used in another infant formula marketed in the United States, manufactured by the same manufacturer, and the manufacturer can demonstrate that such infant formula meets the quality factor requirements prescribed in Sec. 106.96;

106.97(~~b~~a)(2)(ii) The protein source, including any processing methods used to produce the protein source, is not a major change from the infant formula it replaces, and the manufacturer can demonstrate that the infant formula it replaces meets the quality factor requirements prescribed in Sec. 106.96.

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**FDA's Request for Comments on Additional Quality Factors**

IFC Comment

The Agency requested comments whether additional quality factors, specifically for fat, calcium, and phosphorus bioavailability, should be established. Each of these is commented upon below: References are provided in a footnote.

**Fat**: The IFC concurs with FDA that there is no current practical and generally accepted alternative to fat balance studies for assessing total fat bioavailability. Even so, contrary to what is stated in the preamble, fat balance studies are in fact technically difficult to perform well and are conducted at very few research centers.[1] Such studies are much more useful for comparing formulas than for assessing adequacy of a formula, and cross-over designs add much to the sensitivity of this test.[1] Adding to the limitations of these studies is the fact that the level of fat malabsorption which leads to clinical or body composition effects is not well defined and may not be 15%, as stated in the preamble. Furthermore, fat balance studies are relatively invasive, requiring several days of hospitalization. One could argue that this hospitalization was unnecessary and, therefore, unethical. All in all, these studies are not appropriate as quality factor requirements and should continue to be performed only at the discretion of the manufacturer.

**Iron**: Regarding iron, the creation of a quality factor for iron is complicated by the presence in the U.S. market of formulas with varying levels of iron fortification, some of which are nutritionally adequate from the standpoint of iron and others which may not be adequate, but still meet the standards of the Act. It makes little sense to develop a quality factor for a nutrient, which is not required in nutritionally adequate amounts in formulas for healthy infants. This issue generated substantial comment among the members of the FASEB/LSRO panel examining nutrient requirements for infant formulas. No quality factor recommendation is appropriate until and unless the Act is modified to establish a required level of bioavailable iron. Moreover, two factors indicate that any eventual quality factor for iron might better be limited to animal assays of bioavailability, rather than any additional measures incorporated into a standard growth study. Those factors are (a) that the CBC, which may be used to help assess iron nutriture in later infancy, is not sensitive to iron depletion before four months of age when the standard growth study would be conducted,[3] and (b) that the direct measurement of the iron status of infants would require invasive blood tests which are not routine assessments in healthy infants before 9 months of age.[4] We suggest that such studies in infants only be performed when the manufacturer believes they may help assess effects of a specific formula or ingredient.

**Calcium and Phosphorus**: Again, the current state of the art is comparative balance data, but there is a high level of study-to-study and laboratory-to-laboratory variability in the assay.[2] As with fat balance, the use of cross-over designs increases the sensitivity of this test.[1] Given the tendency of balance studies to become more positive with higher intakes, the use of comparable levels of minerals in comparison formulas is generally desirable. Overall, it would be inadvisable to establish a universal quality factor based on the status of this test.[5] Alkaline phosphatase determination would be of no value in balance studies as the time course of its response is slower than the brief period of a balance study. There are also age-specific, gestational and other nutrient effects, which complicate its interpretation. Newer measures of assessing bone mineralization directly hold considerable promise and may

eventually provide the basis for a quality factor when methods become more standardized and more normative data become available for infants. In the meantime, however, there is no measure available, which has demonstrated reliable predictive value.[6-8]

In conclusion, based on the state of the science in each of these areas, the IFC believes that some of the studies discussed may be appropriately used by infant formula manufacturers on a voluntary basis in order to substantiate product claims, but that none of these studies reaches to a level of validity and reliability that would justify its designation as a quality factor requirement at this time. Beyond their scientific status, these additional biochemical indicators would make growth studies much more difficult to perform. Parents and guardians are less likely to consent to and continue participation of their infant in growth studies if blood sampling and other invasive testing are required. Thus, the IFC suggests that such studies only be performed in situations where the manufacturer believes they are necessary to assess specific effects of a formula or ingredient.

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2. Ernst JA, Curse WK, Lemmons JA. Metabolic balance studies in premature infants. Clinics in Perinatology 1995; 22:117-93.
3. Schwartz E., Iron deficiency anemia. *In* Behrman RE, Kliegman RM, Arvin AM eds Nelson Textbook of Pediatrics. WB Saunders Co., Philadelphia, 1996; p 1387.
4. American Academy of Pediatrics. Recommendations for preventive pediatric health care. AAP, Elk Grove, 1995.
5. Avioli LV. Calcium and Phosphorus in Shils ME and Young VR Modern Nutrition. *In* Health and Disease. Lea and Febiger, Philadelphia, 1988; pp 147-149.
6. Picaud J-C, Rigo J., Nyamugabo K., et al. Evaluation of dual-energy x-ray absorptiometry for body-composition assessment in piglets and term human neonates. Am J Clin Nutr 1996; 63: 157-63.
7. Modlesky CM, Lewis RD, Yetman KA, et al. Comparison of body composition and bone mineral measurements from two DXA instruments in young men. Am J Clin Nutr 1996; 64:669-76.
8. Brunton JA, Bayley HS, Atkinson SA. Validation and application of dual-energy x-ray absorptiometry to measure bone mass and body composition in small infants. Am J Clin Nutr 1993; 58: 839-45.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| In newly redesignated subpart F, Sec 106.100 is amended by revising paragraphs (e), (f), (g),(j) and (k)(3), and by removing and reserving paragraph (h) to read as follows: | Acceptable as proposed. |
| **106.100 Records**<br>* * * *<br>106.100(e) *Batch production and control records.* For each batch of infant formula, manufacturers shall prepare and maintain records that include complete information relating to the production and control of the batch. These records shall include but are not limited to: | **106.100 Records**<br>* * * *<br>106.100(e) *Batch production and control records.* For each batch of infant formula, manufacturers shall prepare and maintain records that include complete information relating to the production and control of the batch. The records that are necessary under this paragraph are: |

IFC Redlined Version

106.100(e) *Batch production and control records.* For each batch of infant formula, manufacturers shall prepare and maintain records that include complete information relating to the production and control of the batch. ~~These records shall include but are not limited to:~~ The records that are necessary under this paragraph are:

IFC Comment

See the IFC General Comment regarding Recordkeeping. Regarding the suggested deletion of "but are not limited to," see the IFC General Comment on Recordkeeping for an explanation of the need to focus on only "necessary" records, as dictated in the statute.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(1) The master manufacturing order. The master manufacturing order shall include but is not limited to: | 106.100(e)(1) The master manufacturing order. The master manufacturing order shall include: |
| 106.100(e)(1)(i) The significant steps in the production of the batch and the date on which each significant step occurred; | Acceptable as proposed. |
| 106.100(e)(1)(ii) The identity of equipment and processing lines used in producing the batch, if the plant in which the formula is made includes more than one set of equipment or more than one processing line; | 106.100(e)(1)(ii) The identity of the major equipment systems used in producing the batch, if the plant in which the formula is made includes more than one equipment system; |

IFC Redlined Version

106.100(e)(1) The master manufacturing order. The master manufacturing order shall include ~~but is not limited to~~:

106.100(e)(1)(ii) The identity of the major equipment ~~and processing lines~~ systems used in producing the batch, if the plant in which the formula is made includes more than one ~~set of~~ equipment ~~or more than one processing line~~ system;

IFC Comment

While it is reasonable to require the identity of processing systems and filling lines if more than one are available, it is not reasonable to expect that every transfer line, hook-up station, jumper and valve will be documented. Again, infant formula manufacturing involves multitudes of equipment pieces and lines; the itemization of these for every batch would require significant resources with no practical benefits.

Current procedures document the main equipment that is used to manufacture a batch. However if the operators will need to document all the equipment that is being used, which includes processing lines, tanks, storage containers, and major equipment additional personnel will be needed at a large expense to the manufacturer with no additional benefit to the consumer.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(1)(iii) The identity of each batch or lot of ingredients, containers, and closures used in producing the batch of formula; | Acceptable as proposed. |
| 106.100(e)(1)(iv) The amount of each ingredient to be added to the batch of infant formula and a check (verification) that the correct amount was added; and | Acceptable as proposed. |
| 106.100(e)(1)(v) Copies of all labeling used and the results of examinations conducted during the finishing operations to provide assurance that containers and packages in the lot have the correct label. | 106.100(e)(1)(v) Copies of all primary container labels used and the results of examinations conducted during the finishing operations to provide assurance that containers and packages in the lot have the correct label. |

IFC Redlined Version

106.100(e)(1)(v) Copies of all ~~labeling~~ primary container labels used and the results of examinations conducted during the finishing operations to provide assurance that containers and packages in the lot have the correct label.

IFC Comment

A sample of the primary container label is included in each batch record. However, since larger sized trays, cartons and shippers are also considered labels, their inclusion would substantially increase the size of the batch record. Thus, if all labeling materials were included, a system with significantly more storage space would be needed.

The requirement that all examinations of the packaging materials be retained with the batch records also creates a system and storage problem. All packaging materials are accepted through a packaging acceptance program. Results of the examinations are kept in a separate location, but are easily accessible when necessary. If the results were to be kept in each batch record, additional systems would be needed to combine testing with the batch records. Unnecessarily complicating the batch record may also interfere with the speedy review of those records during production audits and complaint-surveillance.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(2) Any deviations from the master manufacturing order and any corrective actions taken because of the deviations. | 106.100(e)(2) Any deviations from the master manufacturing order and any specific actions taken to adjust or correct a batch in response to a deviation. |

IFC Redlined Version

106.100(e)(2) Any deviations from the master manufacturing order and any ~~corrective~~ specific actions taken to adjust or correct a batch in response to a deviation ~~because of the deviations~~.

IFC Comment

Requiring documentation of any deviations to appear in a batch record is straightforward. Requiring corrective actions to appear in the same batch record would seem to make sense, but may not always be practical over the course of time. If the corrective action is immediate, then its inclusion in the batch record would be expected. However, some deviations require investigation and research over an extended period of time and potentially involve the evaluation of multiple batches before a final corrective action can be agreed upon. In these cases, it would be very unwieldy to put a copy into each of the affected batch records after the fact. However, it is a simple matter to access the relevant corrective actions by other means. If the batch record, deviation report and resulting action, if any, were required to be stored in the same filing system, additional tracking systems would need to be developed, with no commensurate benefit to the public health.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(3) Documentation, in accordance with Sec. 106.6(c), of the monitoring at any point, step, or stage in their production process where control is deemed necessary to prevent adulteration. These records shall include, but not be limited to: | 106.100(e)(3) Documentation, in accordance with Sec. 106.6(c), of the monitoring at any point, step, or stage in their production process where control is deemed critical to prevent adulteration. The records that are necessary under this paragraph shall include: |
| 106.100(e)(3)(i) A list of the standards or specifications established at each point, step, or stage in their production process where control is deemed necessary to prevent adulteration including documentation of the scientific basis for each standard or specification; | 106.100(e)(3)(i) A list of the specifications established at each point, step, or stage in their production process where control is deemed necessary by the manufacturer. |

IFC Redlined Version

106.100(e)(3) Documentation, in accordance with Sec. 106.6(c), of the monitoring at any point, step, or stage in their production process where control is deemed ~~necessary~~ critical to prevent adulteration. ~~These records~~ The records that are necessary under this paragraph shall include~~, but not be limited to~~:

106.100(e)(3)(i) A list of the ~~standards or~~ specifications established at each point, step, or stage in their production process where control is deemed necessary ~~to prevent adulteration including documentation of the scientific basis for each standard or specification;~~ by the manufacturer.

IFC Comment

As discussed in its General Comment entitled "Specifications," its suggested addition of a definition of "specifications" to the regulation and its comment to 106.6(c)(1), the IFC believes that specifications must be allowed to be set at tighter limits than those envisioned in the outer acceptability limits approach. If the FDA does not agree with the IFC's approach and definition for specifications, any inclusion in the final regulation of references to "specifications" will create problems for the IFC members. As discussed earlier in these comments, documentation of the scientific basis for each specification, using an outer-limits approach, would take years of work and would not provide any commensurate benefits to the public health.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(3)(ii) The actual values obtained during the monitoring operation, any deviations from established standards or specifications, and any corrective actions taken; | 106.100(e)(3)(ii) The actual values obtained during the monitoring operation, any deviations from established specifications, and any specific actions taken to adjust or correct a batch in response to a deviation; |

IFC Redlined Version

106.100(e)(3)(ii) The actual values obtained during the monitoring operation, any deviations from established ~~standards or~~ specifications, and any ~~corrective~~ specific actions taken to adjust or correct a batch in response to a deviation;

IFC Comment

See the IFC comments to 106.100(e)(2) and 106.100(e)(3)(i).

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(3)(iii) Identification of the person monitoring each point, step, or stage in their production process where control is deemed necessary to prevent adulteration. | Acceptable as proposed. |
| 106.100(e)(4) The conclusions and follow-up, along with the identity, of the individual qualified by training or experience who investigated: | Acceptable as proposed. |
| 106.100(e)(4)(i) Any deviation from the master manufacturing order and any corrective actions taken; | 106.100(e)(4)(i) Any deviation from the master manufacturing order and any specific actions taken to adjust or correct a batch in response to a deviation; |

IFC Redlined Version

106.100(e)(4)(i) Any deviation from the master manufacturing order and any ~~corrective~~ specific actions taken to adjust or correct a batch in response to a deviation;

IFC Comment

Same comment as noted in 106.100(e)(2).

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(4)(ii) A finding that a batch or any of its ingredients failed to meet the infant formula manufacturer's specifications; and | Acceptable as proposed, subject to the comment below. |

IFC Comment

See the IFC's General Comment regarding "Specifications" and its statements throughout its comments with its concern about the definition and operation of this term. Based on the IFC's belief that permitting tight specifications enhances the quality of infant formula, this language is acceptable so long as tight specifications are permitted by the final regulation and exceeding those tight specifications or standards does not lead to automatic rejection and/or adulteration.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(4)(iii) A failure to meet any specification or standard at any point, step, or stage in the production process where control is deemed necessary to prevent adulteration. | Delete. |

IFC Redlined Version

~~106.100(e)(4)(iii) A failure to meet any specification or standard at any point, step, or stage in the production process where control is deemed necessary to prevent adulteration.~~

IFC Comment

See the IFC's General Comment regarding "Specifications." Also, this proposed language is redundant with (e)(4)(i) above.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(5) The results of all testing performed on the batch of infant formula, including testing on the in-process batch, at the final-product stage, and on finished product throughout the shelf life of the product. The results recorded shall include but are not limited to: | 106.100(e)(5) The results of all testing performed on the batch of infant formula, including testing on the in-process batch, at the final-product stage and on finished product. The results recorded shall include: |

IFC Redlined Version

106.100(e)(5) The results of all testing performed on the batch of infant formula, including testing on the in-process batch, at the final-product stage~~,~~ and on finished ~~product throughout the shelf life of the~~ product. The results recorded shall include ~~but are not limited to~~:

IFC Comment

The requirement to include all stability test results in the individual batch records

represents a large additional administrative burden to current practice of manufacturers and can easily be avoided by requiring that shelf life testing results be made available to the Agency upon request, either by outside communication or by inspection. If a requirement were made to store the data with the manufacturing work order, an additional system would need to be developed to link the data at an additional cost with no commensurate benefit to the public health or additional quality to the product.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(5)(i) The results of all quality control testing conducted, in accordance with Sec. 106.91(a) and (b), to verify that each nutrient required by Sec. 107.100 of this chapter is present in each batch of infant formula at the level required by Sec. 107.100, and that any nutrient added by the manufacturer is present at the appropriate level with: | Acceptable as proposed, subject to the comment below. |
| 106.100(e)(5)(i)(A) A summary table identifying the stages of the manufacturing process at which the nutrient analysis for each required nutrient under §106.91(a) is conducted, and | Acceptable as proposed, subject to renumbering if (B) is deleted as suggested. |
| 106.100(e)(5)(i)(B) A summary table on the stability testing program, including the nutrients tested and the frequency of testing of nutrients throughout the shelf life of the product under Sec. 106.91(b); and | Delete. |

IFC Redlined Version

~~106.100(e)(5)(i)(B) A summary table on the stability testing program, including the nutrients tested and the frequency of testing of nutrients throughout the shelf life of the product under 106.91(b); and~~

IFC Comment

A summary table on the stability testing program results should be required, but its storage limited to inclusion in the file with all shelf life testing results, which may be maintained separate from individual batch records. Also, see the IFC's comment to 106.100(e)(5).

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(e)(5)(ii) For powdered infant formula, the results of any testing conducted in accordance with §106.55(b) to verify compliance with the microbiological quality standards in §106.55(c). | Acceptable as proposed. |
| 106.100(f) Manufacturers shall make and retain all records pertaining to current good manufacturing practice as described in subpart B of this part, including but not limited to: | 106.100(f) Manufacturers shall make and retain all the following necessary records pertaining to current good manufacturing practice as described in subpart B of this part: |

IFC Redlined Version

106.100(f) Manufacturers shall make and retain all the following necessary records pertaining to current good manufacturing practice as described in subpart B of this part~~, including but not limited to~~:

IFC Comment

See the IFC's General Comment to Recordkeeping.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(f)(1) Records, in accordance with §106.20(f)(3), of the frequency and results of testing of the water used in the production of infant formula; | Acceptable as proposed. |
| 106.100(f)(2) Records, in accordance with §106.30(d), of accuracy checks of instruments and controls. A certification of accuracy of any known reference standard used and a history of recertification shall be maintained. At a minimum, such records shall specify the instrument or control being checked, the date of the accuracy check, the standard used, the calibration method used, the results found, any actions taken if the instrument is found to be out of calibration, and the initials or name of the individual performing the test. If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification or standard at a point, step, or stage in the production process where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and any actions that need to be taken with respect to that product, shall be made. | 106.100(f)(2) Records, in accordance with §106.30(d), of accuracy checks of instruments and controls. A certification of accuracy of any known reference standard used and a history of recertification shall be maintained. At a minimum, such records shall specify the instrument or control being checked, the date of the accuracy check, the standard used, the calibration method used, the results found, any actions taken if the instrument is found to be out of calibration, and the initials or name of the individual performing the test. If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification at a point, step, or stage in the production process where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and any actions that need to be taken with respect to that product, shall be made. |
| 106.100(f)(3) Records, in accordance with §106.30(e)(3)(ii), of the temperatures monitored for cold storage compartments and thermal processing equipment. | Acceptable as proposed. |
| 106.100(f)(4) Records, in accordance with Sec. 106.30(f), on equipment cleaning, sanitizing, and maintenance that show the date and time of such cleaning, sanitizing, and maintenance and the lot number of each batch of infant formula processed between equipment start-up and shutdown for cleaning, sanitizing, and maintenance. The person performing and checking the cleaning, sanitizing, and maintenance shall date and sign or initial the record indicating that the work was performed. | 106.100(f)(4) Records, in accordance with Sec. 106.30(f), on equipment cleaning, sanitizing and critical maintenance that show the date and time of such cleaning, sanitizing and critical maintenance. The person performing and checking the cleaning, sanitizing and critical maintenance shall date and sign or initial the record indicating that the work was performed. |

IFC Redlined Version

106.100(f)(2) Records, in accordance with §106.30(d), of accuracy checks of instruments and controls. A certification of accuracy of any known reference standard used and a history of recertification shall be maintained. At a minimum, such records shall specify the instrument or control being checked, the date of the accuracy check, the standard used, the calibration method used, the results found, any actions taken if the instrument is found to be out of calibration, and the initials or name of the individual performing the test. If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification ~~or standard~~ at a point, step, or stage in the production process where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and any actions that need to be taken with respect to that product, shall be made.

106.100(f)(4) Records, in accordance with Sec. 106.30(f), on equipment cleaning, sanitizing,

and critical maintenance that show the date and time of such cleaning, sanitizing, and critical maintenance ~~and the lot number of each batch of infant formula processed between equipment startup and shutdown for cleaning, sanitizing, and maintenance~~. The person performing and checking the cleaning, sanitizing, and critical maintenance shall date and sign or initial the record indicating that the work was performed.

IFC Comment

The proposed requirement to document all lot numbers of batches produced between all equipment cleaning, sanitizing and maintenance is an overwhelming administrative requirement that is not needed on a day to day basis. Certainly the records should have sufficient detail and reference points (time, location, etc.) to allow reconstruction of this type of information if needed. It is a current practice in all manufacturing facilities to clean, sanitize and maintain equipment and utensils, as needed to prevent adulteration of infant formulas at regular intervals defined by the manufacturing facility. Review of all cleaning and sanitizing of CIP'd systems is currently in place. Maintenance of equipment is ongoing and is not necessarily recorded for all equipment. If manufacturers were required to record all maintenance, regardless of whether it is part of a critical process, as well as the lot number of the relevant batches manufactured between the times of maintenance, this would add significant cost to the manufacturing process with no added benefit or safety to the customer. The additional documentation that would be needed to record all of the cleaning, sanitizing and maintenance along with relevant batches manufactured during that time, would require an entirely new tracking system at an very large cost.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(f)(5) Records, in accordance with Sec. 106.35(c), on all automatic (mechanical or electronic) equipment used in the production or quality control of infant formula. These records shall include but not be limited to: | Delete<br>or<br>106.100(f)(5) Records, in accordance with Sec. 106.35(c), on all automatic (mechanical or electronic) equipment used in the production or quality control of infant formula. These records shall include: |

IFC Redlined Version

Delete
or
106.100(f)(5) Records, in accordance with Sec. 106.35(c), on all automatic (mechanical or electronic) equipment used in the production or quality control of infant formula. These records shall include ~~but not be limited to~~:

IFC Comment

See the IFC General Comments regarding Validation and comments on 106.35 where the IFC recommends that any validation provisions of the proposal be deleted or at least postponed. On the basis of IFC's suggestion, it has suggested deletion of all recordkeeping related to validation. If the suggestion to delete is not accepted, see the IFC's General Comment to Recordkeeping regarding the suggested revision to the proposal's language.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(f)(5)(i) A list of all systems used with a description of computer files and the inherent limitations of each system; | Delete. |
| 106.100(f)(5)(ii) A copy of all software used; | Delete. |
| 106.100(f)(5)(iii) Records that document installation, calibration, testing or validation, and maintenance of the systems used; | Delete. |
| 106.100(f)(5)(iv) A list of all persons authorized to create or modify software; | Delete. |
| 106.100(f)(5)(v) Records that document modifications to software, including the identity of the person who modified the software; | Delete. |
| 106.100(f)(5)(vi) Records that document retesting or revalidation of modified systems; and | Delete. |
| 106.100(f)(5)(vii) A backup file of data entered into a computer or related system. The backup file shall consist of a hard copy or alternative system, such as duplicate diskettes, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss. | Delete. |

IFC Redlined Version

~~106.100(f)(5)(i) A list of all systems used with a description of computer files and the inherent limitations of each system;~~

~~106.100(f)(5)(ii) A copy of all software used;~~

~~106.100(f)(5)(iii) Records that document installation, calibration, testing or validation, and maintenance of the systems used;~~

~~106.100(f)(5)(iv) A list of all persons authorized to create or modify software;~~

~~106.100(f)(5)(v) Records that document modifications to software, including the identity of the person who modified the software;~~

~~106.100(f)(5)(vi) Records that document retesting or revalidation of modified systems; and~~

~~106.100(f)(5)(vii) A backup file of data entered into a computer or related system. The backup file shall consist of a hard copy or alternative system, such as duplicate diskettes, tapes, or microfilm, designed to ensure that backup data are exact and complete, and that they are secure from alteration, inadvertent erasures, or loss.~~

IFC Comment

See the IFC's comments to 106.35 and to 106.100(f)(5).

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(f)(6) Records, in accordance with §106.40(g), on ingredients, containers, and closures used in the manufacture of infant formula. These records shall include, but are not limited to: | 106.100(f)(6) Records, in accordance with §106.40(g), on ingredients, containers, and closures used in the manufacture of infant formula. The records that are necessary under this paragraph are: |

IFC Redlined Version

106.100(f)(6) Records, in accordance with 106.40(g), on ingredients, containers, and closures used in the manufacture of infant formula. The records that are necessary under this paragraph are ~~These records shall include, but are not limited to~~:

IFC Comment

See the IFC's General Comment concerning Recordkeeping.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(f)(6)(i) The identity and quantity of each lot of ingredients, containers, and closures; | Acceptable as proposed. |
| 106.100(f)(6)(ii) The name of the supplier; | Acceptable as proposed. |
| 106.100(f)(6)(iii) The supplier's lot numbers; | Acceptable as proposed. |
| 106.100(f)(6)(iv) The name and location of the manufacturer of the ingredient, container, and closure, if different from the supplier; | Acceptable as proposed. |
| 106.100(f)(6)(v) The date of receipt; | Acceptable as proposed. |
| 106.100(f)(6)(vi) The receiving code as specified; and | Acceptable as proposed. |
| 106.100(f)(6)(vii) The results of any test or examination (including retesting and reexamination) performed on the ingredients, containers, and closures and the conclusions derived there from and the disposition of all ingredients, containers, or closures. | Acceptable as proposed. |
| 106.100(f)(7) A full description of the methodology used to test powdered infant formula to verify compliance with the microbiological quality standards of §106.55(c) and the methodology used to do quality control testing, in accordance with §106.91(a) and (b). | Acceptable as proposed. |
| None. | 106.100(f)(8) Results of stability testing performed pursuant to 106.91(b)(2). |
| 106.100(g) The manufacturer shall maintain all records pertaining to distribution of the infant formula, including records that show that products produced for export only are exported. Such records shall include, but not be limited to, all information and data necessary to effect and monitor recalls of the manufacturer's infant formula products in accordance with subpart E of part 107 of this chapter. | 106.100(g) The manufacturer shall maintain all records pertaining to the manufacturer's distribution of the infant formula, including records for products produced for export only. The records required under this paragraph are those providing the information and data necessary to effect and monitor recalls of the manufacturer's infant formula products in accordance with subpart E of part 107 of this chapter. |

IFC Redlined Version

106.100(f)(8) Results of stability testing performed pursuant to 106.91(b)(2).

106.100(g) The manufacturer shall maintain all records pertaining to the manufacturer's distribution of the infant formula, including records ~~that show that~~ for products produced for export only ~~are exported. Such records shall include, but not be limited to, all~~. The records required under this paragraph are those providing the information and data necessary to effect and monitor recalls of the manufacturer's infant formula products in accordance with subpart E of part 107 of this chapter.

IFC Comment

It is reasonable to expect the manufacturer to maintain distribution records regarding shipment of infant formula under the manufacturer's control. Once into the retailer/customer/consumer/exporter's hands, the manufacturer can no longer be responsible for obtaining or keeping these records. The IFC believes that the Agency did not intend to

suggest that the manufacturer had responsibility after product left its control, and requests confirmation of that in the preamble to the final rule.

The FDA should also realize that sometimes manufacturers ship to a customer who, in turn, intends it for export only. Because the manufacturer is not responsible for the actual exportation, the manufacturer would have no records regarding distribution of the material after it is turned over to the exporter.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.100(h) [Reserved]<br>* * * * * | |
| 106.100(j) The manufacturer shall make and retain records pertaining to regularly scheduled audits, including the audit plans and procedures, the findings of the audit, and a listing of any changes made in response to these findings. The manufacturer shall make readily available for authorized inspection the audit plans and procedures and a statement of assurance that the regularly scheduled audits are being conducted. The findings of the audit and any changes made in response to these findings shall be maintained for the time period required under §106.100(n), but need not be made available to FDA. | Acceptable as proposed. |
| 106.100(k)(3) When there is a reasonable possibility of a causal relationship between the consumption of an infant formula and an infant's death, the manufacturer shall, within 15 days of receiving such information, conduct an investigation and notify the agency as required in Sec. 106.150. | 106.100(k)(3) When there is a reasonable possibility of a causal relationship between the consumption of an infant formula and an infant's death, the responsible party shall, within 15 days of receiving such information, conduct an investigation and notify the agency as required in Sec. 106.150. |

IFC Redlined Version

106.100(k)(3) When there is a reasonable possibility of a causal relationship between the consumption of an infant formula and an infant's death, the ~~manufacturer~~ responsible party shall, within 15 days of receiving such information, conduct an investigation and notify the agency as required in Sec. 106.150.

IFC Comment

See the IFC's General Comment regarding Definition of Manufacturer. For this type of notification (as for a new infant formula submission or verification), any duplication of the responsible party's efforts by co-packers would serve no useful purpose.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| **Subpart G--Registration, Submission, and Notification Requirements**<br><br>**106.110 New infant formula registration.**<br><br>106.110(a) Before a new infant formula may be introduced or delivered for introduction into interstate commerce, the manufacturer of such formula shall register with the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS-455), Infant Formula Coordinator, 200 C St. SW, Washington, DC 20204. An original and two copies of this registration shall be submitted. | **Subpart G--Registration, Submission, and Notification Requirements**<br><br>**106.110 New infant formula registration.**<br><br>Acceptable as proposed subject to the Comment below. |

IFC Comment

The IFC's recommended changes are indicated below under the specific proposed provision to which each relates. The IFC recognizes that there may be multiple registrations submitted to FDA in cases where multiple manufacturers/responsible parties are involved in a manufacturing operation. However, there are potential benefits in having all parties involved in infant formula manufacturing operations known to FDA, and because the registration process accomplishes this, the IFC has not suggested that it be changed.

| FDA Proposed Regulation | IFC Suggested Language |
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| 106.110(b) The new infant formula registration shall include:<br><br>106.110(b)(1) The name of the new infant formula, | Acceptable as proposed.<br><br>Acceptable as proposed. |
| 106.110(b)(2) The name of the manufacturer, | 106.110(b)(2) The name of the manufacturer and of the responsible party if other than the manufacturer, |
| 106.110(b)(3) The place of business of the manufacturer, and | 106.110(b)(3) The place of business of the manufacturer and of the responsible party if other than the manufacturer, and |
| 106.110(b)(4) All establishments at which the manufacturer intends to manufacture such new infant formula. | 106.110(b)(4) The names and addresses of all establishments at which the manufacturer or responsible party intends to manufacture such new infant formula. |

IFC Redlined Version

106.110(b)(2) The name of the manufacturer and of the responsible party if other than the manufacturer,

106.110(b)(3) The place of business of the manufacturer~~,~~ and of the responsible party if other than the manufacturer, and

106.110(b)(4) ~~All~~ The names and addresses of all establishments at which the manufacturer

or responsible party intends to manufacture such new infant formula.
IFC Comment

The IFC believes that FDA would benefit from knowing when a co packer or ancillary manufacturer is involved. Therefore, it suggests that a manufacturer be asked to identify the responsible party who contracted its services. Similarly, responsible parties should be asked to identify all the manufacturers it will use. While the registration form that FDA develops probably will require names and addresses, it is preferable to make it required information.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| **106.120 New infant formula submission.**<br><br>106.120(a) At least 90 days before a new infant formula is introduced or delivered for introduction into interstate commerce, a manufacturer shall submit notice of its intent to do so to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies of the notice of its intent to do so shall be submitted. | **106.120 New infant formula submission.**<br><br>106.120(a) At least 90 days before a new infant formula is introduced or delivered for introduction into interstate commerce, a responsible party shall submit notice of its intent to do so to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies of the notice of its intent to do so shall be submitted. |

IFC Redlined Version

106.120(a) At least 90 days before a new infant formula is introduced or delivered for introduction into interstate commerce, a ~~manufacturer~~ responsible party shall submit notice of its intent to do so to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies of the notice of its intent to do so shall be submitted.

IFC Comment

For a new infant formula, duplicate notifications by manufacturer's and co-packers would serve no useful purpose.

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| FDA Proposed Regulation | IFC Suggested Language |
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| 106.120(b) The new infant formula submission shall include:<br><br>106.120(b)(1) The name and physical form (e.g., powder, ready-to feed, or concentrate) of the infant formula;<br><br>106.120(b)(2) An explanation of why the formula is a new infant formula; | Acceptable as proposed.<br><br>Acceptable as proposed.<br><br>Acceptable as proposed. |
| 106.120(b)(3) The quantitative formulation of each form of the infant formula that is the subject of the notice in units per volume (for liquid formulas) or units per dry weight (for powdered formulas). When applicable, the submission shall include a description of any reformulation of the infant formula, including a listing of each new or changed ingredient and a discussion of the effect of such changes on the nutrient levels in the formulation; | Acceptable as proposed subject to the comment below. |

IFC Comment

The Agency proposes that quantitative formulations be submitted in units/volume for liquids. Contrary to the preamble statement that infant formula manufacturers have such a listing as part of the master manufacturing order, formulations are routinely listed and have traditionally been submitted to the Agency in units/weight. However, although it will require the use of conversion factors, the formulations can be submitted in units/volume if so desired.

The term "quantitative formulation" needs to be defined. Does it still envision a table of nutrients as well as a table of ingredients? The IFC recommends against changing to units/volume (for liquids) or units per dry weight (for powders) for a nutrient table, since the per 100 kcal format is already generated for label use and is easy to compare across product forms. If the change to units/volume or units per dry weight is finalized, FDA needs to clarify what volume or weight should be used as the denominator (100 ml, liter, kilo?) and whether the information should be provided "as sold" or "as fed."

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| FDA Proposed Regulation | IFC Suggested Language |
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| 106.120(b)(4) A description, when applicable, of any change in processing of the infant formula. Such description shall identify the specific change in processing, including side-by-side, detailed schematic diagrams comparing the new processing to the previous processing (including processing times and temperatures); | 106.120(b)(4) A description, when applicable, of any significant change in processing of the infant formula. |

IFC Redlined Version

106.120(b)(4) A description, when applicable, of any change in processing of the infant formula. ~~Such description shall identify the specific change in processing, including side-by-side, detailed schematic diagrams comparing the new processing to the previous processing (including processing times and temperatures);~~

IFC Comment

To date, a narrative description of the change has been acceptable. A general schematic is also provided showing the current process and the revised process if appropriate, however, times and temperatures have not been included. The schematic allows changes to be highlighted for a complete review of the change to occur. Mandating side-by-side, detailed schematic diagrams of current and new systems, including times, temperatures, etc. would require substantial amounts of additional administrative support to the current level needed to prepare submissions. If the infant formula manufacturer were to meet this new request for times and temperatures on the schematic, a new document system would need to be designed to develop and track the flow diagrams. This would require new computer programs and additional resources with no added safety to the customer.

| FDA Proposed Regulation | IFC Suggested Language |
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| 106.120(b)(5) Assurance that the infant formula will not be marketed unless the formula meets the quality factor requirements of section 412(b)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and the nutrient content requirements of section 412(i) of the act. | Acceptable as proposed. |
| 106.120(b)(5)(i) Assurance that the formula meets the quality factor requirements, which are set forth in subpart E of this part, shall be provided by a submission that complies with Sec. 106.121. | Acceptable as proposed. |
| 106.120(b)(5)(ii) Assurance that the formula complies with the nutrient content requirements, which are set forth in §107.100 of this chapter, shall be provided by a statement assuring that the formula will not be marketed unless it meets the nutrient requirements of §107.100 of this chapter, as demonstrated by testing required under subpart C of this part; | Acceptable as proposed. |

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| None. | 106.120(b)(6)(i) A responsible party that has not previously manufactured infant formula for sale in the U.S. market must support the premarket notification with a clinical study.<br><br>106.120(b)(6)(ii) Clinical studies also may be necessary when a current manufacturer or responsible party predicts, based on its experience or theory, that a major change could have possible significant adverse impact on bioavailability of nutrients and when chemical testing or other scientific information are unavailable to rule out such an adverse impact.<br><br>106.120(b)(6)(iii) The manufacturer shall determine the scope, degree and complexity of any needed clinical testing, on a case-by-case basis. The particular elements of the study shall take into account Guidelines issued by FDA regarding clinical study protocol and design and endpoints needed to support potential claims. |

IFC Redlined Version

106.120(b)(6)(i) A responsible party that has not previously manufactured infant formula for sale in the U.S. market must support the premarket notification with a clinical study.

106.120(b)(6)(ii) Clinical studies also may be necessary when a current manufacturer or responsible party predicts, based on its experience or theory, that a major change could have possible significant adverse impact on bioavailability of nutrients and when chemical testing or other scientific information are unavailable to rule out such an adverse impact.

106.120(b)(6)(iii) The manufacturer shall determine the scope, degree and complexity of any needed clinical testing, on a case-by-case basis. The particular elements of the study shall take into account Guidelines issued by FDA regarding clinical study protocol and design and endpoints needed to support potential claims.

IFC Comments

There are certain circumstances in which a premarket notification should include a clinical study demonstrating the bioavailability of the infant formula. Indeed, the industry and the agency collectively developed guidelines in 1986 that defined "major changes" and established a framework for ascertaining whether a clinical study would be advisable for demonstrating the bioavailability of nutrients in a new or reformulated infant formula. *FDA, Guidelines Concerning Notification and Testing of Infant Formulas*, 1986. Congress recognized the wisdom of these 1986 guidelines by incorporating them into the 1986 Amendments to the Infant Formula Act. The Infant Formula Act provides that "for purposes of this paragraph, the term 'major change' has the meaning given to such term in section 106.30(c)(2) of title 21, Code of Federal Regulations (as in effect on August 1, 1986), *and guidelines issued thereunder.*" FFDCA § 412(c)(2) *(emphasis added)*. The phrase "*guidelines issued thereunder*" is a direct reference to the 1986 Guidelines. The

incorporation of the 1986 Guidelines into the statutory language restricts the agency's ability to deviate from the well-established principles contained in those guidelines.

The 1986 Guidelines define "major change" and provide examples of the changes in formulation and/or processing that would be viewed as a major change. The 1986 Guidelines also establish the following recommendations for clinical studies for new and reformulated infant formulas.

> FDA has recognized that premarket clinical evaluation in humans may be appropriate whenever certain changes affecting the nutritional profile of an infant formula are made, particularly in the case of new or reformulated products. FDA has also recognized that the degree and complexity of the clinical testing needed will vary according to the extent of the changes in the formula. Until guidelines are developed, it is therefore understood that the scope of the clinical testing necessary for new and reformulated infant formulas will be decided by the manufacturer on a case-by-case basis and that the chemical testing alone for major reformulation may not be sufficient to determine adequacy of the product.

The new proposed 106.120(b)(6) is modeled after the regulatory framework established by the 1986 Guidelines and sanctioned by Congress through the incorporation of these guidelines in the Infant Formula Act. The rationale for placement of the proposed regulations regarding clinical studies in section 106.120 for 90-day notifications stems directly from the 1986 amendments to the Infant Formula Act. The Infant Formula Act incorporates the 1986 Guidelines in section 412(c)(2), the section that defines "new infant formulas" that would require the submission of a premarket notification. Congress notably did not include this reference to the 1986 Guidelines in the section of the Infant Formula Act that addressed quality factors (FFDCA § 412(b)(1)) or the section regarding the inclusion in infant formula premarket notifications of data demonstrating that the infant formula meets the quality factor requirements (FFDCA § 412(d)(1)(C)). The incorporation of the 1986 Guidelines in Section 412(b)(2) further supports the IFC position that growth should not be defined as a quality factor that would be demonstrated through clinical studies.

The proposed section 106.120(b)(6) includes clinical studies as part of the data and information that would, when necessary, be included in a premarket notification. This is accomplished, not by defining growth as a quality factor and mandating clinical studies demonstrating growth—as proposed by FDA—but by including a provision in section 106 identifying the instances in which clinical studies should be included in a premarket notification. The new section 106.120(b)(6) provisions proposed by industry codify the industry and agency practices that have been in place for almost two decades and that have proven effective in assuring the integrity of infant formulas.

The new section 106.120(b)(6)(i) would require a responsible party that has not previously manufactured infant formula for sale in the U.S. to include the results of a clinical study in the premarket notification. This proposed provision reflects the well-established FDA practice of requiring a new responsible party to conduct a clinical study demonstrating that the company is capable of complying with the stringent formulation and manufacturing requirements before entering the U.S. infant formula market. Infant formulas are unique food products in that the infant formula generally provides the only source of nutrition for a young infant. The manufacturer must have practices and procedures in place to make certain that

the infant formula will provide all of the nutrients needed for the growing infant in a biologically available form and matrix. In addition, the vulnerability of the infant population to disease and infection requires adherence to strict sanitation, quality and other standards. By requiring a new responsible party to conduct a clinical study before entering the market place, the agency can be assured that the new responsible party will be capable of producing an infant formula that supports growth. The new section 106.120(b)(6)(i) reflects this well-established practice by mandating a clinical study for a new responsible party that has not previously manufactured infant formula in the United States.

The new proposed section 106.120(b)(6)(ii) recognizes that clinical studies may be necessary to support a premarket notification for a "major change" submitted by a manufacturer or responsible party that is currently marketing an infant formula in the United States. A clinical study would be conducted when the manufacturer's experience or theory would predict a possible significant adverse impact on the bioavailability of nutrients in the new or reformulated infant formula and when chemical testing or other scientific information are unavailable to rule out the possibility of such an adverse impact. This standard is similar, although not identical, to the definition of "major change" found in the 1986 Guidelines. Industry experience has demonstrated that a clinical study is not needed to support every "major change" in formulation and/or processing. The industry experience has shown, however, that some "major changes" are of a sufficient magnitude or nature to require evaluation in a clinical study to make certain that the change will not have a significant adverse impact on the bioavailability of nutrients in the infant formula.

The final provision of the new proposed regulation, section 106.120(b)(6)(iii), would clarify that it is up to the manufacturer to determine the scope, degree, and complexity of the clinical study on a case-by-case basis. This provision incorporates the standard established by the 1986 Guidelines and recognizes that the manufacturer is in the best position to assess the likely impact on nutrient bioavailability of the proposed "major change" to the infant formula and the type of study that will be needed to support such a change. The proposed regulatory provision also would recognize that the manufacturer should conduct any such clinical study in accordance with clinical study, protocol and design guidelines that would be issued by the agency.

In conclusion, the new proposed sections 106.120(b)(6)(i), (ii), and (iii), would codify into the regulations the practices and procedures that have been in-place since 1986. These practices and procedures are based on the language found in the 1986 Guidelines, which have been incorporated by reference into the Infant Formula Act. Importantly, the standard created by the 1986 Guidelines and which IFC proposes to codify in the final regulations, provides the flexibility that is needed for ascertaining when a clinical study should be conducted. There have been numerous innovations to infant formulas since 1986. The industry has proven that it can responsibly evaluate proposed major changes to formulations and determine whether the change requires a clinical study to assess the impact of the change on the bioavailability of the nutrients in the infant formula.

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| 106.120(b)(6) Assurance that the processing of the infant formula complies with section 412(b)(2) of the act. Such assurance shall include but not be limited to: | Acceptable; Renumbered as 106.120(b)(7). |
| 106.120(b)(6)(i) A statement that the formula will be produced in accordance with subparts B and C of this part; | Acceptable; Renumbered as 106.120(b)(7)(i). |
| 106.120(b)(6)(ii) The basis on which each ingredient meets the requirements of Sec. 106.40(a), e.g., that it is an approved food additive, that it is authorized by a prior sanction issued by the agency, or that it is GRAS for its intended use. Any claim that an ingredient is GRAS shall be supported by a citation to the agency's regulations or by an explanation, including a list of published studies and a copy of those publications, for why, based on the published studies, there is general recognition of the safety of the use of the ingredient in infant formula. | Delete. |

IFC Redlined Version

106.120(b)(~~6~~7) Assurance that the processing of the infant formula complies with section 412(b)(2) of the act. Such assurance shall include but not be limited to:

106.120(b)(~~6~~7)(i) A statement that the formula will be produced in accordance with subparts B and C of this part;

~~106.120(b)(6)(ii) The basis on which each ingredient meets the requirements of 106.40(a), e.g., that it is an approved food additive, that it is authorized by a prior sanction issued by the agency, or that it is GRAS for its intended use. Any claim that an ingredient is GRAS shall be supported by a citation to the agency's regulations or by an explanation, including a list of published studies and a copy of those publications, for why, based on the published studies, there is general recognition of the safety of the use of the ingredient in infant formula.~~

IFC Comment

The IFC believes that this section should be deleted. See the IFC Comment to 106.40(a) and it's General Comments regarding Premarket Notification and Redundancy. The Agency's proposal constitutes premarket approval of the ingredients used in infant formulas, i.e., such ingredients must be demonstrated safe to the Agency's satisfaction that an ingredient is GRAS for its intended use. The IFC respectfully but strongly disagrees with FDA's legal interpretation. In promulgating the Infant Formula Act, Congress clearly intended that the law be used to ensure that the manufacturer produce formulas that meet the Infant Formula Act nutrient composition requirements and that are not contaminated with substances or organisms that might adulterate the product. Congress did not intend to give FDA premarket approval authority over infant formula. Nor did it need or intend to give FDA additional premarket approval authority, beyond that already given FDA under Sections 402 and 409 of the FFDCA, over food ingredients employed in formula.

21 CFR 170.30 describes requirements for independent GRAS determinations, as well as the requirements under which FDA will affirm, in response to voluntary applications,

that an ingredient is GRAS; however, 21 CFR 170.30 in no way mandates that the information the manufacturer is relying upon be submitted to the Agency or formally acknowledged or listed as GRAS. Of course, in many or most cases manufacturers will, in the interest of reducing regulatory uncertainties, find it in their own self-interest to submit such information; however, such submissions should remain voluntary, as they always have been. It should remain proper for the manufacturer to go to market without submitting this information, just as it remains the manufacturer's responsibility to ensure the safety and suitability of its individual infant formula products.

Finally, if FDA retains this language in modified form to remove the premarket approval objection, the word "newly added" should be inserted before "ingredient" to make it clear that the information provided to FDA need not relate to all ingredients in the infant formula.

IFC would like to remind the Agency that it is of critical importance to keep the purpose of the Infant Formula Act in perspective. The Infant Formula Act really was an effort, arising directly out of troublesome nutrient delivery failures, to ensure the nutritional quality of infant formula. It is in this specific context that the fundamental affirmative requirements of the Infant Formula Act take on meaning. For example, the quality factor, GMP, record retention, testing, in-process controls among just a few of the IFA's requirements *all* reasonably relate to ensuring the *nutritional quality* of infant formula. The Infant Formula Act in this context is, thus, an "overlay" on FDA's already substantial authority provided by the FFDCA to ensure the safety and proper labeling of food. It is that underlying Act that continues to provide the critical tools for ensuring the safety of infant formula.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.120(c) For products for export only, a manufacturer may submit, in lieu of the information required under paragraph (b) of this section, a statement that the infant formula meets the specifications of the foreign purchaser, does not conflict with the laws of the country to which it is intended for export, is labeled on the outside of the shipping package to indicate that it is intended for export only, and will not be sold or offered for sale in domestic commerce. | 106.120(c) For products for export only and in compliance with Section 801(e) of the Act, the information under paragraph (b) of this section is not required and need not be submitted. |

IFC Redlined Version

106.120(c) For products for export only and in compliance with Section 801(e) of the Act, the information under paragraph (b) of this section is not required and need not be submitted~~, a manufacturer may submit, in lieu of the information required under paragraph (b) of this section, a statement that the infant formula meets the specifications of the foreign purchaser, does not conflict with the laws of the country to which it is intended for export, is labeled on the outside of the shipping package to indicate that it is intended for export only, and will not be sold or offered for sale in domestic commerce~~.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer and Infant Formulas Intended For Export.

IFC believes this provision is adequately covered under the FDA Export Reform Enhancement Act (Public Law 104-134, as amended Public Law 104-180) and the resultant regulations 21 CFR Part 1 entitled "Exports: Notification and Recordkeeping Requirements."

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.120(d) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(c) and (d) of the act. | 106.120(d) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will notify the submitter within 10 working days if the notice is not complete because it does not meet the requirements of section 412(c) and (d) of the act. |

IFC Redlined Version

106.120(d) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will notify the submitter within 10 working days if the notice is not ~~adequate~~ complete because it does not meet the requirements of section 412(c) and (d) of the act.

IFC Comment

Manufacturers who make a new infant formula submission under 106.120 need certainty for planning purposes. If FDA's notice of inadequacy is received well into what has been planned to be a 90-day review period, the planning process will be seriously disrupted. Accordingly, a submission should get immediate review for completeness.

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| FDA Proposed Regulation | IFC Suggested Language |
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| 106.120(e) If a new infant formula submission is adequate, FDA will acknowledge its receipt and notify the manufacturer of the date of receipt. The date that the agency receives the new infant formula submission is the filing date for the submission. The manufacturer shall not market the new infant formula before the date that is 90 days after the filing date. | 106.120(e) If a new infant formula submission is complete and includes all requirements of 106.120(b), FDA will acknowledge its receipt and notify the submitter of the date of the receipt. The date that the agency receives the new infant formula submission is the filing date for the submission. The manufacturer shall not market the new infant formula before the date that is 90 days after the filing date. |

IFC Redlined Version

106.120(e) If a new infant formula submission is ~~adequate~~ complete and includes all requirements of 106.120(b), FDA will acknowledge its receipt and notify the ~~manufacturer~~ submitter of the date of the receipt. The date that the agency receives the new infant formula submission is the filing date for the submission. The manufacturer shall not market the new infant formula before the date that is 90 days after the filing date.

IFC Comment

See the IFC General Comment regarding Premarket Notification. The IFC is concerned that the Agency might wish to delay the starting date for the 90-day period when the notification is complete, but there are questions or disagreement with the content. The act requires that manufacturers give a 90-day advance notice to the Agency prior to marketing a new infant formula. Unlike drugs, there are no explicit pre-market approval requirements for infant formula. While the IFC agrees that the notification must be complete and understandable, and the product must satisfy the nutritional requirements for the intended use, the marketing of an infant formula should not be held up while the Agency takes issue with some minor elements of the notification.

The IFC believes that the 90-day clock must begin when the Agency receives a notification that supplies information for all paragraphs listed in 106.120. Running of the 90 day clock should be based on completeness, and not on the Agency's immediate judgment of agreement with the contents. If there are questions or concerns regarding the content of the notification, these should be worked out between the Agency and the manufacturer after the 90-day clock has started.

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| FDA Proposed Regulation | IFC Suggested Language |
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| 106.120(f) If the manufacturer provides additional information in support of a new infant formula submission, the agency will determine whether the additional information is a substantive amendment to the new infant formula submission. If the agency determines that the new submission is a substantive amendment, FDA will assign the new infant formula submission a new filing date. FDA will acknowledge receipt of the additional information and, when applicable, notify the manufacturer of the new filing date, which is the date of receipt by FDA of the information that constitutes the substantive amendment to the new infant formula submission. | 106.120(f) If the submitter provides additional information in support of a new infant formula submission, the agency will determine whether the additional information is a substantive amendment to the new infant formula submission. If the agency determines that the new submission is a substantive amendment, FDA will assign the new infant formula submission a new filing date. FDA will acknowledge receipt of the additional information within five working days and, when applicable, notify the submitter of the new filing date, which is the date of receipt by FDA of the information that constitutes the substantive amendment to the new infant formula submission. |

IFC Redlined Version

106.120(f) If the ~~manufacturer~~ submitter provides additional information in support of a new infant formula submission, the agency will determine whether the additional information is a substantive amendment to the new infant formula submission. If the agency determines that the new submission is a substantive amendment, FDA will assign the new infant formula ~~submission a new filing date. FDA will acknowledge receipt of the additional information~~ within five working days and, when applicable, notify the ~~manufacturer~~ submitter of the new filing date, which is the date of receipt by FDA of the information that constitutes the substantive amendment to the new infant formula submission.

IFC Comment

The IFC suggestion to refer to a "submitter" will cover both manufacturers and responsible parties. The five-day provision reflects the IFC's belief that the Agency must be bound by some reasonable time requirements, so that manufacturers can plan appropriately.

| FDA Proposed Regulation | IFC Suggested Language |
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| **106.121 Quality factor submission.**<br><br>To provide assurance that an infant formula meets the quality factor requirements set forth in subpart E of this part, the manufacturer shall submit the following data and information: | **106.121 Quality factor submission.**<br><br>To provide assurance that a new infant formula meets the quality factor requirements set forth in subpart E of this part, the responsible party shall submit the following data and information: |

IFC Redlined Version

To provide assurance that ~~an~~ a new infant formula meets the quality factor requirements set forth in subpart E of this part, the ~~manufacturer~~ responsible party shall submit the following data and information:

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. For this type of submission any duplication of the responsible party's efforts by co-packers would serve no useful purpose. The IFC has also suggested adding the word "new" to clarify that these two requirements apply only to new infant formulas as defined in these regulations.

U.S. Infant Formula Manufacturers developed the attached "Decision Tree for Documentation of Nutritional Adequacy of a New or Changed Infant Formula" (Attachment K) and "Decision Tree Chart for Documentation of Nutritional Adequacy of a New or Changed Infant Formula" (Attachment L) in 2002. These documents discuss various changes to infant formula and the documentation required for such changes to support nutritional adequacy.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.121(a) An explanation, in narrative form, setting forth how all quality factor requirements of subpart E of this part have been met. | Acceptable as proposed. |
| 106.121(b) Records that contain the information required by proposed Sec. 106.97(a)(1)(i) and (a)(1)(ii) collected during the study for each infant enrolled in the study. The records shall be identified by subject number, age, feeding group, gender, and study day of collection. | Delete. |

IFC Redlined Version

~~106.121(b) Records that contain the information required by proposed Sec. 106.97(a)(1)(i) and (a)(1)(ii) collected during the study for each infant enrolled in the study. The records shall be identified by subject number, age, feeding group, gender, and study day of collection.~~

IFC Comment

Regarding IFC's recommended deletion of these proposed regulations, see General Comments on Assessment of Normal Growth. IFC offers comments on all the following proposed regulations falling under section 106.121(a) with the caveat that clinical growth studies only should be included in a premarket notification consistent with the new section 106.120(b)(6) proposed by IFC. The specifics as to the nature and scope of such a study, as well as the presentation of resulting data, should be incorporated into agency Guidance rather than a regulation.

See the IFC's comments to 106.97(a)(1). The IFC has no objection to submitting individual growth data whenever a growth study has been determined to be the most appropriate demonstration of bioavailable and sufficient nutrition. However, IFC would like to take this opportunity to point out some potential pitfalls in interpreting those data.

It is fairly straightforward to carry out statistical analysis of growth variables for each formula feeding group. However, it is more difficult, and at times impossible, to draw valid

conclusions about an individual or a small subgroup of individuals within a formula feeding group. Growth data are expected to be normally distributed; consequently, there will always be a few infants who will be at the lower or upper end of a particular growth parameter. By presenting growth data on individuals, unwarranted attention may be brought to these infants at the extremes of the data distribution. There may be undue concern that every infant did not demonstrate *average* growth patterns. There may also be undue concern that the characteristics of these individuals are representative of a significant subgroup of the sample.

For these reasons, it would ensure a better focus on the key analysis of a clinical study if the manufacturer were able to present growth data to FDA simply as group statistics and not as growth data for individual study infants. IFC realizes, however, that group statistics alone will not, as a rule, provide enough detail to satisfy the Agency that no adverse consequences may be attributable to use of the new formula. Consequently, we ask that the preamble of the final rule make clear that it is the group statistics that provide the primary basis for the manufacturer's finding that expected physical growth has been attained, and that the growth data for individual study infants will be reviewed by the Agency only as supportive data to demonstrate that there was no significant subgroup within the sample for which the formula had adverse effects.

The IFC also suggests that the preamble acknowledge that the "records" contemplated by 106.121(b) need not be the investigator's original records, but may instead be records that contain the necessary information drawn from the investigators' original records.

| FDA Proposed Regulation | IFC Suggested Language |
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| 106.121(c)(1) Statistical evaluation for all measurements, including: Group means, group standard deviations, and measures of statistical significance for all measurements for each feeding group at the beginning of the study and at every point where measurements were made throughout the study. | Delete. |
| 106.121(c)(2) Calculation of the statistical power of the study at its completion. | Delete. |

IFC Redlined Version

~~106.121(c)(1) Statistical evaluation for all measurements, including: Group means, group standard deviations, and measures of statistical significance for all measurements for each feeding group at the beginning of the study and at every point where measurements were made throughout the study.~~

~~106.121(c)(2) Calculation of the statistical power of the study at its completion.~~

IFC Comment

As would be codified under 106.97(a)(1)(ii)(E) of the proposed regulations, the need for a power calculation arises *before* a study is initiated, in order to determine the number of study subjects required to answer a clinical question. Because subject dropout may be predicted for most clinical studies, various strategies are employed to achieve the desired

number of subjects at study conclusion such as over enrollment or replacement of dropouts. In some situations fewer subjects are available for clinical study or complete a clinical study than originally anticipated. It is reasonable to expect from a study report that: a) there was an *a priori* calculation of the power of the study, b) the number of subjects to be recruited met the needs of the power calculation, and c) whether the number of subjects who actually completed the study corresponded to this need.

It is necessary and of unproven value to require a calculation of the power of a study at its completion. This is clearly a *post-hoc* analysis. It is also a confounding and burdensome calculation to make, as there may be several parameters with multiple time points with differing numbers of subjects for each variable and time point. The IFC recommends, accordingly, that FDA not require such a calculation in the context of submission to FDA of clinical study results, since there is no general scientific consensus that this practice is necessary or appropriate.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.121(d) A report on attrition and on all occurrences of adverse events during the study, which shall include: | Delete. |
| 106.121(d)(1) Identification of the infant by subject number and feeding group and a complete description of the adverse event, including comparisons of the frequency and nature of occurrence in each feeding group and information on the health of the infant during the course of the study, including the occurrence and duration of any illness; | Delete. |
| 106.121(d)(2) A clinical assessment, by a health care provider, of the infant's health during each suspected adverse event; | Delete. |
| 106.121(d)(3) A complete listing of all infants who did not complete the study, including the infant's subject number and the reason that each infant left the study. | Delete. |
| 106.121(e) The results of the Protein Efficiency Ratio, in accordance with Sec. 106.97(b). | Delete. |

IFC Redlined Version

~~106.121(d) A report on attrition and on all occurrences of adverse events during the study, which shall include:~~

~~106.121(d)(1) Identification of the infant by subject number and feeding group and a complete description of the adverse event, including comparisons of the frequency and nature of occurrence in each feeding group and information on the health of the infant during the course of the study, including the occurrence and duration of any illness;~~

~~106.121(d)(2) A clinical assessment, by a health care provider, of the infant's health during each suspected adverse event;~~

~~106.121(d)(3) A complete listing of all infants who did not complete the study, including the infant's subject number and the reason that each infant left the study.~~

~~106.121(e) The results of the Protein Efficiency Ratio, in accordance with Sec. 106.97(b).~~

IFC Comment

The language in section 106.121(d) and its subsections is acceptable, with the caveat that clinical growth studies only should be included in a premarket notification consistent with the new section 106.120(b)(6) proposed by IFC. For the reasons discussed previously, any specifics as to the nature and scope of such a study, as well as the presentation of resulting data, should be incorporated into agency Guidance rather than a regulation.

The effect of the proposed 106.121(d) would be to mandate the submission of test results for biological quality of the protein 90 days before the new infant formula is to be marketed. (See proposed 106.121(e)). The IFC agrees with the requirement for PER or other

testing to demonstrate protein quality and the circumstances in which it is required. However, the IFC disagrees with the time that the results of this testing are due.

Under current regulations, protein results need not be submitted at the time of the 90-day submission, but can be submitted along with the verification submission that is filed subsequent to the 90-day submission. (See 106.30(c)(2)). This timing is particularly significant when new equipment triggers the 90-day premarket requirement. As stated above, under current regulations, protein testing can be deferred and can be performed on product that has been produced on the newly installed equipment. The proposed regulation would instead require protein test results to be submitted at the time of the 90-day premarket submission without apparent exception.

Where PER testing is used, requiring protein testing to be submitted with the 90 day premarket submission effectively accelerates the needed start of testing by 5 months (three months premarket and two months of test time). This will force the manufacturer either to delay the start-up with the new equipment by 5 months or choose to determine and convince FDA that the research production system is "close enough" to the full scale system to be representative of product produced on the full scale production equipment.

The timing of submittal of the protein testing results created by the proposal could delay improvements and add significant additional costs to infant formula. This will be detrimental to the public and not add value to infant formula. Therefore, it would be in the best interest of consumers to allow the results of protein-quality testing to be included with the verification test results as they are currently without known adverse events.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.121(f) A statement certifying that the manufacturer has collected and considered all information and data concerning the ability of the infant formula to meet the quality factor requirements, and that the manufacturer is not aware of any information or data that would show that the formula does not meet the quality factors requirements. | 106.121(b) A statement of assurance that the manufacturer or responsible party has collected and considered all information and data concerning the ability of the infant formula to meet the quality factor requirements, and that the manufacturer or responsible party is not aware of any information or data that would show that the formula does not meet the quality factors requirements. |

IFC Redlined Version

106.121(~~f~~b) A statement ~~certifying~~ of assurance that the manufacturer or responsible party has collected and considered all information and data concerning the ability of the infant formula to meet the quality factor requirements, and that the manufacturer or responsible party is not aware of any information or data that would show that the formula does not meet the quality factors requirements.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. The suggested use of "assurance" is based on the provisions of the Infant Formula Act relating to verifications that refer specifically to "assurances," as opposed to certifications. (See, e.g.,

412(d)(1)(C)&(D).

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| **106.130 Verification submission.**<br><br>106.130(a) Manufacturers shall, after the first production and before the introduction into interstate commerce of the new infant formula, verify in a written submission to FDA at the address given in Sec. 106.110(a), that the infant formula complies with the requirements of the Federal Food, Drug, and Cosmetic Act (the act) and is not adulterated. An original and two copies of this verification shall be submitted. | **106.130 Verification submission.**<br><br>106.130(a) Unless subject to 106.120(c) [proposed by IFC to be moved and become 106.140(d)], manufacturers or responsible parties shall, after the first production and before the introduction into interstate commerce of the new infant formula, verify in a written submission to FDA at the address given in Sec. 106.110(A), that the infant formula complies with the requirements of the act and is not adulterated. An original and two copies of this verification shall be submitted. |

IFC Redlined Version

106.130(a) Unless subject to 106.120(c) [proposed by IFC to be moved and become 106.140(d)], ~~M~~manufacturers or responsible parties shall, after the first production and before the introduction into interstate commerce of the new infant formula, verify in a written submission to FDA at the address given in Sec. 106.110(a), that the infant formula complies with the requirements of the ~~Federal Food, Drug, and Cosmetic Act (the act)~~ and is not adulterated. ~~An original and two copies of this verification shall be submitted.~~

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. For this type of submission, any duplication of the responsible party's efforts by co-packers would serve no useful purpose.

See the IFC's General Comment concerning Infant Formulas Intended For Export. The proposed language does not exempt infant formulas intended for export. Because such formulas are exempt from GMPs and other requirements of the act, such a submission will serve no purpose. Therefore, infant formula intended for export only should clearly be exempt from this section.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.130(b) The verification submission shall include the following information:<br><br>106.130(b)(1) The name of the new infant formula; the filing date for the new infant formula submission, in accordance with Sec. 106.120, for the subject formula; and the identification number assigned by the agency to the new infant formula submission; | Acceptable as proposed.<br><br>106.130(b)(1) The name of the new infant formula; the filing date for the new infant formula submission, in accordance with Sec. 106.120, for the subject formula; and the identification number assigned by the agency, if available, to the new infant formula submission; |

IFC Redlined Version

106.130(b)(1) The name of the new infant formula; the filing date for the new infant formula submission, in accordance with Sec. 106.120, for the subject formula; and the identification number assigned by the agency, if available, to the new infant formula submission;

IFC Comment

This number may not in all cases have been assigned or be available, so providing the qualifier acknowledges this possibility.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.130(b)(2) A statement that the infant formula to be introduced into interstate commerce is the same as the infant formula that was the subject of the new infant formula notification and for which the manufacturer provided assurances in accordance with the requirements of Sec. 106.120; | 106.130(b)(2) A statement that the infant formula to be introduced into interstate commerce is the same as the infant formula that was the subject of the new infant formula notification and for which the manufacturer or responsible party provided assurances in accordance with the requirements of Sec. 106.120; |

IFC Redlined Version

106.130(b)(2) A statement that the infant formula to be introduced into interstate commerce is the same as the infant formula that was the subject of the new infant formula notification and for which the manufacturer or responsible party provided assurances in accordance with the requirements of Sec. 106.120;

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.130(b)(3) A summary of test results of the level of each nutrient required by §107.100 of this chapter and any nutrient added by the manufacturer in the formula, presented in units per 100 kilocalories at the final-product-stage. | Acceptable as proposed. |
| None. | 106.130(b)(4) If testing for protein biological quality is needed, an assurance that the PER or other test has commenced, and that the results will be forwarded to FDA within 10 working days of their receipt by the manufacturer or responsible party as a supplement to the verification submission. |
| 106.130(b)(4) A certification that the manufacturer has established current good manufacturing practices including quality control procedures and in-process controls, including testing required by current good manufacturing practice, designed to prevent adulteration of this formula in accordance with subparts B and C of this part. | 106.130(b)(5) An assurance by the responsible party that all manufacturers have established current good manufacturing practices including quality control procedures and in-process controls, including testing required by current good manufacturing practice, designed to prevent adulteration of this formula in accordance with subparts B and C of this part. |

IFC Redlined Version

106.130(b)(4) If testing for protein biological quality is needed, an assurance that the PER or other test has commenced, and that the results will be forwarded to FDA within 10 working days of their receipt by the manufacturer or responsible party as a supplement to the verification submission.

106.130(b)(45) ~~A certification that the manufacturer has~~ An assurance by the responsible party that all manufacturers have established current good manufacturing practices including quality control procedures and in-process controls, including testing required by current good manufacturing practice, designed to prevent adulteration of this formula in accordance with subparts B and C of this part.

IFC Comment

In reference to section 106.30(b)(3), all nutrients are tested at the finished product stage of major change batches. A notification indicating the batch complies is sent to the FDA. If the proposed change is accepted, additional information will need to be prepared to send to the FDA.

See the IFC Comment to proposed 106.121(e) for the basis for the suggested new language regarding protein quality, its comment to 121(f) for use of the term "assurance."

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.130(c) The submission will not constitute written verification under section 412(d)(2) of the act when any data prescribed in paragraph (b) of this section are lacking or are not set forth so as to be readily understood. In such circumstances the agency will notify the submitter that the notice is not adequate. | 106.130(c) The submission will not constitute written verification under section 412(d)(2) of the act when any data prescribed in paragraph (b) of this section are lacking or are not set forth so as to be readily understood. In such circumstances the agency will notify the submitter within five working days that the notice is not complete. |

IFC Redlined Version

106.130(c) The submission will not constitute written verification under section 412(d)(2) of the act when any data prescribed in paragraph (b) of this section are lacking or are not set forth so as to be readily understood. In such circumstances the agency will notify the submitter within five working days that the notice is not ~~adequate~~ complete.

IFC Comment

FDA should be required to notify manufacturers within five working days when their verifications are unacceptable. Otherwise, manufacturers will not be able to market their product with assurance that FDA found the submission acceptable. The IFC also recommends that the FDA develop a form for verifications that will help in FDA's review of the sufficiency of the verification.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| **106.140 Submission concerning a change in infant formula that may adulterate the product.**<br><br>106.140(a) When a manufacturer makes a change in the formulation or processing of the formula that may affect whether the formula is adulterated under section 412(a) of the Federal Food, Drug, and Cosmetic Act (the act), it shall, before the first processing of such formula, make a submission to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies shall be submitted. | **106.140 Submissions for Minor Changes in the Infant Formula.**<br><br>106.140(a) When a manufacturer makes a change in the formulation or processing of the formula that is determined to be a notifiable minor change because the manufacturer or responsible party determines it may affect whether the formula is adulterated under section 412(a) of the act, it shall, before the first processing of such formula, make a submission to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies shall be submitted. |

IFC Redlined Version

**106.140 Submissions for Minor Changes in the Infant Formula ~~concerning a change in infant formula that may adulterate the product.~~**

106.140(a) When a manufacturer makes a change in the formulation or processing of the formula that is determined to be a notifiable minor change because the manufacturer or responsible party determines it may affect whether the formula is adulterated under section 412(a) of the ~~Federal Food, Drug, and Cosmetic Act (the act)~~ act, it shall, before the first processing of such formula, make a submission to the Food and Drug Administration at the address given in Sec. 106.110(a). An original and two copies shall be submitted.

IFC Comment

The IFC believes that the suggested wording will help clarify what conduct constitutes a "major change," and what constitutes a "minor change."

IFC also requests FDA to clarify that minor changes made to infant formulas intended solely for export are not subject to the notification requirements of this provision.

Additionally, FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with proposal. Infant formula manufacturers currently evaluate all changes to formulation or processing of an infant formula. In that assessment they determine if the change will affect the nutrient content of the formulation and if so, notify the FDA. In the preamble of the proposed GMP's, FDA has provided examples of changes they would consider notifiable changes requiring testing at the required intervals. If the manufacturer is now required to notify all of these types of changes, this will increase the amount of submissions drastically, and additional personnel will be needed. (See also 106.3(i)(5))

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.140(b) The submission shall include:<br><br>106.140(b)(1) The name and physical form of the infant formula (i.e., powder, ready-to-feed, or concentrate); | Acceptable as proposed.<br><br>Acceptable as proposed. |
| 106.140(b)(2) An explanation of why the change in formulation or processing may affect whether the formula is adulterated; | 106.140(b)(2) An explanation of why the change may affect whether the formula is adulterated and assurance that the formula will not be introduced into interstate commerce unless it is not adulterated; |

IFC Redlined Version

106.140(b)(2) An explanation of why the change ~~in formulation or processing~~ may affect whether the formula is adulterated and assurance that the formula will not be introduced into interstate commerce unless it is not adulterated;

IFC Comment

The addition of the information requested in (ii) will enable FDA to receive a more complete explanation of the change.

| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.140(b)(3) A submission that complies with §106.120(b)(3), (b)(4), (b)(5), and (b)(6). When appropriate, a statement to the effect that the information required by §106.120(b)(3), (b)(4), (b)(5), or (b)(6) has been provided to the agency previously and has not been affected by the changes that is the subject of this submission, together with the identification number assigned by the agency to the relevant infant formula submission, may be provided in lieu of such submission. | Acceptable as proposed. |
| 106.140(c) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the act. | 106.140(c) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will promptly acknowledge receipt and notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the act. |
| None. | 106.140(d) The requirements of 106.140 do not apply to products legally exported under §801(e) of the act. |

IFC Redlined Version

106.140(c) The submission will not constitute notice under section 412 of the act unless it complies fully with paragraph (b) of this section, and the information that it contains is set forth in a manner that is readily understandable. The agency will promptly acknowledge receipt and notify the submitter if the notice is not adequate because it does not meet the requirements of section 412(d)(3) of the act.

106.140(d) The requirements of 106.140 do not apply to products legally exported under §801(e) of the act.

IFC Comment

FDA should be required to notify manufacturers within one week, or within some other reasonable period of time, of whether their verifications are acceptable. Otherwise, manufacturers will not be able to market their product with assurance that FDA found the submission acceptable.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| **106.150 Notification of an adulterated or misbranded infant formula.**<br><br>106.150(a) A manufacturer shall promptly notify FDA in accordance with paragraph (b) of this section, when the manufacturer has knowledge (that is, the actual knowledge that the manufacturer had, or the knowledge which a reasonable person would have had under like circumstances or which would have been obtained upon the exercise of due care) that reasonably supports the conclusion that an infant formula that has been processed by the manufacturer and that has left an establishment subject to the control of the manufacturer: | **106.150 Notification of an adulterated or misbranded infant formula.**<br><br>106.150(a) A manufacturer or responsible party shall promptly notify FDA in accordance with paragraph (b) of this section, when the manufacturer or responsible party has knowledge (that is, the actual knowledge that the manufacturer or responsible party had, or the knowledge which a reasonable person would have had under like circumstances or which would have been obtained upon the exercise of due care) that reasonably supports the conclusion that an infant formula that has been processed by the manufacturer or responsible party and that has left an establishment subject to the control of the manufacturer or responsible party: |

IFC Redlined Version

106.150(a) A manufacturer or responsible party shall promptly notify FDA in accordance with paragraph (b) of this section, when the manufacturer or responsible party has knowledge (that is, the actual knowledge that the manufacturer or responsible party had, or the knowledge which a reasonable person would have had under like circumstances or which would have been obtained upon the exercise of due care) that reasonably supports the conclusion that an infant formula that has been processed by the manufacturer or responsible party and that has left an establishment subject to the control of the manufacturer or responsible party:

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. For this type of submission any duplication of the responsible party's efforts by co-packers would serve no useful purpose.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.150(a)(1) May not provide the nutrients required by section 412(i) of the act or by regulations issued under section 412(i)(2); or<br><br>106.150(a)(2) May be otherwise adulterated or misbranded. | Acceptable as proposed.<br><br>106.150(a)(2) May be otherwise adulterated or misbranded. In the case of "adulteration" based on a failure to follow GMPs, the failure must be of such a nature as to reasonably call into question the suitability of the formula. Notification shall not be required for minor or technical misbranding. |

IFC Redlined Version

106.150(a)(2) May be otherwise adulterated or misbranded. In the case of "adulteration" based on a failure to follow GMPs, the failure must be of such a nature as to reasonably call into question the suitability of the formula. Notification shall not be required for minor or technical misbranding.

IFC Comment

See the IFC General Comment regarding Notification of Adulteration or Misbranding.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 106.150(b) The notification made according to paragraph (a) of this section shall be made by telephone, to the Director of the appropriate Food and Drug Administration district office. After normal business hours (8 a.m. to 4:30 p.m.), FDA's emergency number, 202-857-8400, shall be used. The manufacturer shall send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS-455), Infant Formula Coordinator, 200 C St. SW, Washington, DC 20204, and to the appropriate Food and Drug Administration district office specified in Sec. 5.115 of this chapter. | 106.150(b) The notification made according to paragraph (a) of this section shall be made by telephone, to the Director of the appropriate Food and Drug Administration district office. After normal business hours (8 a.m. to 4:30 p.m.), FDA's emergency number, 202-857-8400, shall be used. The manufacturer or responsible party shall send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS-455), Infant Formula Coordinator, 200 C St. SW, Washington, DC 20204, and to the appropriate Food and Drug Administration district office specified in Sec. 5.115 of this chapter. |

IFC Redlined Version

106.150(b) The notification made according to paragraph (a) of this section shall be made by telephone, to the Director of the appropriate Food and Drug Administration district office. After normal business hours (8 a.m. to 4:30 p.m.), FDA's emergency number, 202-857-8400, shall be used. The manufacturer or responsible party shall send written confirmation of the notification to the Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, Division of Programs and Policy Enforcement (HFS-455), Infant Formula Coordinator, 200 C St. SW, Washington, DC 20204, and to the appropriate Food and Drug Administration district office specified in Sec. 5.115 of this chapter.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer.

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| **107.1 Status and applicability of the regulations in part 107.** | **107.1 Status and applicability of the regulations in part 107.** |
| 107.1(a) The criteria set forth in subpart B of this part describes the labeling requirements applicable to infant formula under section 403 of the Federal Food, Drug, and Cosmetic Act (the act). Failure to comply with any regulation in subpart B of this part will render an infant formula misbranded under that section of the act. Acceptable as proposed. | Acceptable as proposed. |
| 107.1(b) The criteria set forth in subpart C of this part describes the terms and conditions for the exemption of an infant formula from the requirements of section 412(a), (b), and (c) of the act. Failure to comply with any regulations in subpart C of this part will result in the withdrawal of the exemption given under section 412(h)(1) of the act. | Acceptable as proposed. |
| 107.1(c) Subpart D of this part sets forth the nutrient requirements for infant formula under section 412(i) of the act. Failure to comply with any regulation in subpart D of this part will render an infant formula adulterated under section 412(a)(1) of the act. | Acceptable as proposed. |
| **107.10 Nutrient Information.** | **107.10 Nutrient Information.** |
| 107.10(a) * * *<br><br>107.10(a)(2) A statement of the amount, supplied by 100 kilocalories, of each of the following nutrients and of any nutrient added by the manufacturer: | Acceptable as proposed. |
| **107.240 Notification requirements.** | **107.240 Notification requirements.** |
| 107.240(a) Telephone report. When a determination is made that an infant formula is to be recalled, the recalling firm shall telephone within 24 hours the appropriate Food and Drug Administration district office listed in §5.115 of this chapter and shall provide relevant information about the infant formula that is to be recalled. | Acceptable as proposed. |

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| FDA Proposed Regulation | IFC Suggested Language |
|---|---|
| 107.240(b) Initial written report. Within 14 days after the recall has begun, the recalling firm shall provide a written report to the appropriate Food and Drug Administration district office. The report shall contain relevant information, including the following cumulative information concerning the infant formula that is being recalled: | Acceptable as proposed. |
| 107.240(b)(1) Number of consignees notified of the recall and date and method of notification, including recalls required by §107.200, information about the notice provided for retail display and the request for its display. | Acceptable as proposed. |
| 107.240(b)(2) Number of consignees responding to the recall communication and quantity of recalled infant formula on hand at the time it was received. | Acceptable as proposed. |
| 107.240(b)(3) Quantity of recalled infant formula returned or corrected by each consignee contacted and the quantity of recalled infant formula accounted for. | Acceptable as proposed. |
| 107.240(b)(4) Number and results of effectiveness checks that were made. | Acceptable as proposed. |
| 107.240(b)(5) Estimated timeframes for completion of the recall. | Acceptable as proposed. |
| 107.240(c) Status reports. The recalling firm shall submit to the appropriate Food and Drug Administration district office a written status report on the recall at least every 14 days until the recall is terminated. The status report shall describe the steps taken by the recalling firm to carry out the recall since the last report and the results of these steps. | Acceptable as proposed. |
| **107.250 Termination of an infant formula recall** | **107.250 Termination of an infant formula recall** |
| The recalling firm may submit a recommendation for termination of the recall to the appropriate Food and Drug Administration district office listed in §5.115 of this chapter for transmittal to the Division of Enforcement (HFS-605), Office of Field Programs, Center for Food Safety and Applied Nutrition, for action. Any such recommendation shall contain information supporting a conclusion that the recall strategy has been effective. The agency will respond within 15 days of receipt by the Division of Enforcement (HFS-605), Office of Field Programs, Center for Food Safety and Applied Nutrition, of the request for termination. The recalling firm shall continue to implement the recall strategy until it receives final written notification from the agency that the recall has been terminated. The agency will send such notification, unless it has information, from FDA's own audits or from other sources demonstrating the recall has not been effective. The agency may conclude that a recall has not been effective if: | Acceptable as proposed. |

## CONCLUSION

The International Formula Council appreciates the opportunity to comment on this proposal. As stated above, if FDA has any questions or requires clarification of any aspects of this document, it should feel free to contact Mardi Mountford or Robert Gelardi.

Respectfully submitted,

Robert C. Gelardi
President
International Formula Council

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Wyeth Nutrition

RCG/mkm/rs
Enclosures: Attachment A: International Formula Council Suggested Language

Attachment B: FDA Infant Formula GMP Regulation (Redlined against IFC Suggested Edits)

Attachment C: IFC's June 20, 2003 letter to Dr. Christine Taylor re Industry Proposal on Infant Formula Powder Labeling

Attachment D: IFC's June 27, 2003 letter to Dr. Christine Taylor re Proposed Discussion Points on Powdered Infant Formula Good Manufacturing Practices

## CONCLUSION

The International Formula Council appreciates the opportunity to comment on this proposal. As stated above, if FDA has any questions or requires clarification of any aspects of this document, it should feel free to contact Mardi Mountford or Robert Gelardi.

Respectfully submitted,
Robert C. Gelardi for

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Attachment E: IFC's July 7, 2003 letter to Dr. Christine Taylor re Special Products

Attachment F: Douglas L. Archer's July 7, 2003 letter to Robert C. Gelardi re Summary of Industry Data re Testing for *E. sakazakii* in Powdered Infant Formula – Submitted to Dr. Christine Taylor on July, 7, 2003

Attachment G: "Guidelines Concerning Notification and Testing of Infant Formulas" incorporated into section 412(c)(1) of the 1986 Amendments to the Infant Formula Act (hereinafter "1986 Guidelines")

Attachment H: Russell J. Merritt's November 2002 Slide Presentation to FAC

Attachment I: Jon A. Vanderhoof's November 2002 Slide Presentation to FAC

Attachment J: Jose M. Saavedra's November 2002 Slide Presentation to FAC

Attachment K: IFC's "Decision Tree for Documentation of Nutritional Adequacy of a New or Changed Infant Formula" submitted to the FAC in November 2002

Attachment L: IFC's "Decision Tree Chart for Documentation of Nutritional Adequacy of a New or Changed Infant Formula" submitted to FAC in November 2002

Attachment M: IFC's "Sample Clinical Growth Trial Protocol for Healthy Term Infants" submitted to the FAC in November 2002

Attachment N: Robert C. Gelardi's Oral Testimony before the FAC, April 4, 2002

Attachment O: Nutritional Profiles of Infant Formula provided to FASEB by IFC's August 22, 1996 letter